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(54) Title: ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE

(57) Abstract

The present invention describes the use of pyrazole or indazole derivates as activators of soluble guanylate cyclase. Some compounds disclosed are novel. All activators are vasodilators and/or inhibit platelet aggregation and are therefore useful in the treatment of peripheral vascular diseases such as hypertension, angina pectoris or atherosclerosis, or in the treatment of prevention of glaucoma, preeclampsia, Raynaud's syndrome, stroke or erectile disfunctions.

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ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE

This invention relates to activators of soluble guanylate cyclase (sGC), to their preparation and to their use.

Soluble guanylate cyclase is responsible for the enzymatic conversion of guanosine-5'-triphosphate (GTP) to cyclic guanosine-3',5'-monophosphate (cGMP). The enzyme is stimulated by NO binding to the enzyme.

sGC is responsible for numerous physiological processes including vascular and non-vascular smooth muscle relaxation, peripheral and central neurotransmission, platelet reactivity and phototransduction (Hobbs A.J., TiPS, December 1997, Vol 18, p.484). Activators of sGC can therefore be expected to have valuable therapeutic properties.

As explained above, NO is known as an activator of sGC. However, this compound has a number of different physiological effects and its use in activating sGC therefore suffers from a myriad of side effects. There is therefore a need for selective activators of sGC.

3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1) is a known NO independent activator of sGC (Hobbs, A.J., TiPS, December 1997, Vol 18, p.484). However, the activation achieved is not high.

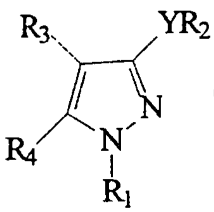
Certain pyrazoles and indazoles are known *per se*. Thus, Palazzo et al, J. Med. Chem. 9, 38 (1966) discloses certain indazoles substituted at the 1- position with alkyl, phenyl or 2-phenylethyl and at the 3- position with $-O(CH_2)_n-NMe_2$ wherein n is 2 or 3. These compounds are said to be analgesics and anti-inflammatory and antispasmodic agents.

FR-A-7505524 discloses particular pyrazoles substituted at the 1- and 4- positions with optionally substituted phenyl groups and at the 3- position with a group $-O-(CH_2)_n-NR_3R_4$ wherein n is 2 or 3 and R_3 and R_4 are various radicals or, together with the N atom to which they are attached, form a heterocyclic ring. Such compounds are also said to be anti-inflammatory agents and analgesics.

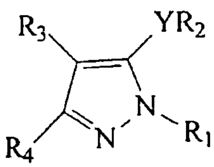
Bull. Chem. Soc. Jpn., 53, 825-826 (1980) discloses 3-(3-Dimethylaminopropyloxy)-1-*H*- indazole as a candidate for an anti-inflammatory drug.

Soga et al, Yuki Gogei Kagaku Kyokai Shi, 28, 437 (1970) discloses 1-(3-Dimethylaminopropyl)-3-(3-dimethylaminopropyloxy)-1*H*-indazole but does not mention any ability to activate sGC.

Accordingly, the present invention provides the use of a compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the activation of soluble guanylate cyclase:



(Ia)



(Ib)

wherein:

Y is: -O-, $-CH_2-$ or -NH-;

R_1 is: hydrogen, aryl, heteroaryl, 3- to 6- membered heterocyclyl, $-(C_1-C_4$ alkyl)-R wherein R is aryl, heteroaryl or 3- to 6- membered heterocyclyl, C_1-C_4 alkyl, $-CONA'_2$, -COA" or $-SO_2A"$ wherein each A' is the same or different and is selected from H, C_1-C_4 alkyl and aryl and each A" is the same or different and is selected from C_1-C_4 alkyl and aryl;

R_2 is: (a) when Y is -O-: $-XNMe_2$ or -XNHMe wherein X is an alkylene group having from 3 to 5 carbon atoms or R_2 is 2-hydroxymethylfuran-5-yl-methyl or -WB wherein W is an alkylene group having from 1 to 5 carbon atoms and B is a N-containing heterocyclic group;

(b) when Y is $-CH_2-$: $-XNMe_2$ or -XNHMe wherein X is as defined above; and

(c) when Y is -NH-: $-XNMe_2$ or -XNHMe wherein X is propylene; and

R_3 and R_4, are either:

(a) the same or different and selected from $-CO_2A'$ wherein A' is as defined above, $-CF_3$, $-CCl_3$, halogen, C_1-C_4 alkoxy, $-(C_1-C_4$ alkyl)-aryl, $-(C_1-C_4$ alkyl)-heteroaryl, hydrogen, C_1-C_4 alkyl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl, $-SO_2NA'_2$ wherein A' is as defined above, or $-CONZ_1Z_2$ wherein Z_1 and Z_2, which are the

same or different, represent H, C_1-C_4 alkyl, aryl, heteroaryl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl or -(C_1-C_4 alkyl)-R wherein R is aryl, heteroaryl, 3- to 6- membered heterocyclyl or C_3-C_6 carbocyclyl, or Z_1 and Z_2, together with the nitrogen atom to which they are attached, denote a 5- or 6- membered N-containing heterocyclic group; or

(b) different, one of R_3 and R_4 being aryl or heteroaryl and the other being as defined above;

or R_1 and R_2 are as defined above and R_3 and R_4 together form the divalent group, -$(CH)_4$-, which group is optionally substituted.

A C_1-C_4 alkyl group or moiety can, unless specified otherwise, be linear or branched but is preferably linear. Suitable such alkyl groups and moieties include methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl. Methyl is preferred. Unless specified otherwise, a C_1-C_4 alkyl group or moiety can be substituted or unsubstituted at any position. Typically, it carries up to 3 substituents. Suitable substituents include C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, hydroxy, halogen, -CF_3, -CCl_3, -NA'_2, -CO_2A' or -NH-CO-(C_1-C_4 alkyl) in which A' is as defined above. Preferred substituents are halogen, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, dimethylamino, -NH-CO-CH_3, -CO_2H and -CO_2Me.

A C_1-C_4 alkoxy group is typically a said C_1-C_4 alkyl group attached to an oxygen atom.

A C_1-C_4 haloalkyl or haloalkoxy group is typically a said C_1-C_4 alkyl or alkoxy group substituted by one or more halogen atoms. Typically, it is substituted by one, two or three halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as -CX_3 and -OCX_3 wherein X is a halogen atom. Particularly preferred haloalkyl groups are CF_3 and CCl_3. Particularly preferred haloalkoxy groups are -OCF_3 and -$OCCl_3$.

A -(C_1-C_4 alkyl)-aryl group is typically a said C_1-C_4 alkyl group joined to an aryl group, as defined below. It is preferably benzyl or 2-phenylethyl.

A halogen atom is typically a chlorine, fluorine, bromine or iodine atom. It is preferably chlorine.

An aryl group or moiety is typically a C_6-C_{10} aryl group or moiety. Suitable such aryl groups and moieties include phenyl and naphthyl. Phenyl is preferred. An aryl group or moiety may be substituted or unsubstituted at any position.

Typically, an aryl group or moiety carries 1, 2, 3 or 4 substituents. Suitable substituents include aryl, for example phenyl, heteroaryl, 3- to 6- membered heterocyclyl, C_3-C_6 carbocyclyl, -(C_1-C_4 alkyl)-aryl, for example benzyl, -(C_1-C_4 alkyl)-heteroaryl, halogen, nitro, cyano, hydroxyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio such as methylthio or ethylthio, $-NA'_2$, $-CO_2A'$ and -NH-CO-A' in which A' is as defined above and -COA″ wherein A″ is as defined above.

Preferred heteroaryl and heterocyclic substituents are 5- or 6- membered heteroaryl or heterocyclic rings containing 1, 2 or 3 heteroatoms selected from N, O and S. Examples include thiadiazole, for example 1,2,3-thiadiazole, thiazole, imidazole, isoxazole, isothiazole, furan, pyrazole, pyrrole and thiophene substituents. Other preferred substituents include phenyl, methyl, ethyl, methoxy, ethoxy, hydroxy, nitro, cyano, dimethylamino, methylthio, ethylthio, $-NH-CO-CH_3$ and -CO-(C_1-C_4 alkyl).

An aryl group may optionally be fused to a further said aryl group, to a C_3-C_6 carbocyclic group, to a heteroaryl group, for example a pyrrole group or a thiadiazole group such as a 1,2,5-thiadiazole group, or to a 3- to 6- membered heterocyclic group, for example a 1,4-dioxolane group, for example a 5,5-difluoro-1,4-dioxolane group, a tetrahydrofuran group, for example a 2,2-dimethyl-tetrahydrofuran group, or a pyrrolidine group, for example a 2,5-dioxo-pyrrolidine group. A preferred pyrrolidine group is a 1-methyl-2,5-dioxopyrrolidine group.

The alkylene group X typically has 3 or 4 carbon atoms. It may be unsubstituted or substituted at any position. Typically it is unsubstituted or monosubstituted. When Y is $-CH_2$- or -NH-, X is typically unsubstituted α to the amine moiety. Suitable substituents include C_1-C_4 alkyl such as methyl or ethyl.

The alkylene group W typically has from 2 to 4 carbon atoms. It may be substituted or unsubstituted at any position. Typically, it is unsubstituted or monosubstituted. Suitable substituents include C_1-C_4 alkyl such as methyl or ethyl.

A C_3-C_6 carbocyclic group is a non-aromatic saturated or unsaturated

hydrocarbon ring having from 3 to 6 carbon atoms. Preferably, it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclohexyl.

A C_3-C_6 carbocyclic group may be fused to a said aryl group, to a further C_3-C_6 carbocyclic group or to a heteroaryl or 3- to 6- membered heterocyclyl group.

A C_3-C_6 carbocyclic group may be unsubstituted or substituted at any position. Typically, it carries up to 3 substituents. Suitable substituents include halogen, hydroxyl, nitro, cyano, CF_3, CCl_3 C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 alkylthio such as methylthio or ethylthio, -NA'$_2$, -CO$_2$A' and -NH-CO-A' in which A' is as defined above or -COA$''$ wherein A$''$ is as defined above. Preferred substituents include methyl, ethyl, methoxy, ethoxy, hydroxy, dimethylamino, and -NH-CO-CH_3.

A heteroaryl group is typically a 5- to 10- membered aryl ring containing at least one heteroatom selected from O, S and N. It may be unsubsituted or substituted at any position. Typically, it carries up to three substituents. Suitable substituents include aryl, for example phenyl, heteroaryl, 3- to 6- membered heterocyclyl, C_3-C_6 carbocyclyl, -(C_1-C_4 alkyl)-aryl, for example benzyl, -(C_1-C_4 alkyl)-heteroaryl, halogen, hydroxyl, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio such as methylthio and ethylthio, nitro, cyano, -COA$''$ wherein A$''$ is as defined above, -NA'$_2$, -CO$_2$A' and -NH-CO-A' in which A' is as defined above. Preferred substituents include phenyl, benzyl, methyl, ethyl, methoxy, ethoxy, hydroxy, dimethylamino and -NH-CO-CH_3.

Preferably, the heteroaryl group is a 5- or 6- membered ring.

Suitable heteroaryl groups include thiadiazolyl, for example 1,2,3-thiadiazolyl and 1,2,5-thiadiazolyl, oxadiazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyridyl, furanyl, thienyl, pyrazolidinyl, pyrazolyl and pyrrolyl groups. Preferred are oxadiazolyl, pyrazolyl, pyridyl, imidazolyl, furanyl, thienyl and pyrrolyl.

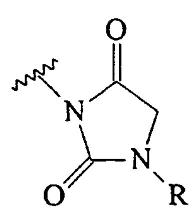
A heteroaryl group may optionally be fused to a said aryl group, for example to a phenyl group, to a said C_3-C_6 carbocyclic group, for example to a cyclohexyl

group, to a further heteroaryl group or to a 3- to 6- membered heterocyclic group. Example of such fused heteroaryl groups include quinoline, and thiazole and imidazole groups fused to phenyl or cyclohexyl groups. Particularly preferred fused heteroaryl groups are quinoline groups.

A 3- to 6- membered heterocyclic group may be a substituted or unsubstituted 3- to 6- membered ring containing at least one heteroatom selected from N, O and S. It typically contains one, two or three such heteroatoms. A 3- to 6- membered heterocyclic group may be fused to a said aryl, heteroaryl or C_3-C_6 carbocyclic group or to a further 3- to 6- membered heterocyclic group.

A 3- to 6- membered heterocyclic group typically carries up to 3 substituents. Suitable substituents include oxo, aryl, for example phenyl, heteroaryl, -(C_1-C_4 alkyl)-aryl for example benzyl, -(C_1-C_4 alkyl)-heteroaryl, halogen, hydroxyl, CF_3, CCl_3 C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, -NA'$_2$, -CO_2A' and -NH-CO-A' in which A' is as defined above. Preferred substituents include oxo, aryl, -(C_1-C_4 alkyl)-aryl, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, dimethylamino, and -NH-CO-CH_3.

Suitable 3- to 6- membered heterocyclic groups include 1,4-dioxolane, tetrahydrofuran, pyrrolidyl, pyrazolidinyl, piperidyl, piperazinyl and hydantoin groups. Preferred heterocyclic groups are 2,5-dioxopyrrolidinyl groups and N linked hydantoin groups of the formula



wherein R is a C_1-C_4 alkyl group or a (C_1-C_4 alkyl)-aryl group.

The N-containing heterocyclic group B may be an unsubstituted or substituted, saturated or unsaturated,-5- or 6-membered N-containing ring.

Suitable substituents include oxo, halogen, hydroxyl, CF_3, CCl_3, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, -NA'$_2$, -CO_2A' and -NH-CO-A' in which A' is as defined above. Preferred substituents include methyl,

ethyl, methoxy, ethoxy, hydroxy, amino, dimethylamino and $-NH-CO-CH_3$.

The ring may optionally include one or two more heteroatoms selected from N, O and S. Suitable rings include pyridyl, piperidyl, pyrrolidinyl, piperazinyl, imidazolyl and imidazolinyl. The N-containing heterocyclic group may therefore be a 2-pyridyl, 3-piperidyl, 2-pyrrolidinyl, 1-pyrrolidinyl, 4-piperazinyl or 2-imidazolyl group. A ring may be substituted on a N-atom as appropriate by a C_1-C_4 alkyl group such as a methyl group.

Alternatively, the N-containing heterocyclic group B may be a fused ring system such as a said unsubstituted or substituted, saturated or unsaturated, 5- or 6-membered N-containing ring fused to an aryl group such as a benzene ring. The benzene ring may itself be substituted or unsubstituted. Suitable substituents for the benzene ring include halogen, hydroxyl, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, $-NA'_2$, $-CO_2A'$ and NH-CO-A' in which A' is as defined above. A suitable such N-containing heterocyclic group fused to a benzene ring is a benzimidazolyl group such as a benzimidazol-2-yl group. The benzimidazolyl group is typically substituted at any position on the benzene ring by halogen.

Typically, the number of carbon atoms in the alkylene group W and the position at which the group B is attached to the -W- group are such that the N atom of the N- containing heterocyclic group B is spaced from the group Y by from 3 to 5 atoms, preferably by 3 or 4 atoms.

The 5- or 6- membered N-containing heterocyclic ring formed by Z_1, Z_2 and the nitrogen atom to which Z_1 and Z_2 are attached may be a saturated or unsaturated such ring. Suitable substituents include oxo, halogen, hydroxyl, nitro, cyano, CF_3, CCl_3, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 alkylthio such as methylthio or ethylthio, $-NA'_2$, $-CO_2A'$ or -NH-CO-A' in which A' is as defined above and -COA″ wherein A″ is as defined above. Preferred substituents include methyl, ethyl, methoxy, ethoxy, hydroxy, amino, dimethylamino and $-NH-CO-CH_3$. The ring may optionally contain one or two more heteroatoms selected from N, O and S. Suitable rings include N-morpholino, N-piperazino and N-piperidino rings.

Preferably, Y is -O-.

Each A' is preferably hydrogen, methyl or phenyl and each A" is preferably methyl or phenyl.

When R_1 is a C_1-C_4 alkyl group or a group -(C_1-C_4 alkyl)-R, it is typically unsubstituted at the α position or substituted at the α position other than by a methyl group.

When R_1 is an aryl group or a -(C_1-C_4 alkyl)-aryl group, the aryl group or moiety is typically a phenyl group or moiety or a phenyl group or moiety fused to a 3- to 6- membered heterocyclic group such as a 1,4-dioxolane group. Preferred substituents on the aryl group or moiety include aryl such as phenyl, halogen, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, nitro and cyano.

When R_1 is a heteroaryl group or a -(C_1-C_4 alkyl)-heteroaryl group the heteroaryl group or moiety is typically an imidazolyl, thiazolyl, thienyl, pyrrolyl or furyl group or moiety. Preferred substituents on the heteroaryl group or moiety include aryl such as phenyl, -(C_1-C_4 alkyl)-aryl such as benzyl or chlorobenzyl, halogen, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl and C_1-C_4 haloalkyl.

Preferably R_1 is hydrogen; aryl, for example phenyl, heteroaryl, -(linear C_1-C_4 alkyl)-R in which the alkyl moiety is unsubstituted at the α position and R is aryl, for example phenyl, or heteroaryl, for example imidazolyl or thienyl, or R_1 is linear C_1-C_4 alkyl optionally substituted other than at the α position with hydroxy, halogen, $-CF_3$, $-CCl_3$, $-NA'_2$, $-CO_2A'$ or -NH-CO-(C_1-C_4 alkyl), or R_1 is $-CONA'_2$; -COA" or $-SO_2A"$; wherein A' and A" are as defined above.

More preferably, R_1 is hydrogen, -(CH_2)-aryl, for example benzyl, -(CH_2)-heteroaryl, for example $-CH_2$-imidazolyl or $-CH_2$-thienyl, aryl, for example phenyl, 3-hydroxy-n-propyl, 3-dimethylamino-n-propyl, 2-phenylethyl, 2-(CO_2Me)-ethyl, $-CONMe_2$, -COMe, -COPh or $-SO_2Me$.

Still more preferably, R_1 is hydrogen, phenyl, benzyl, -(CH_2)-R wherein R is imidazolyl or thienyl, or -CO-phenyl.

R_2 is preferably $-XNMe_2$ wherein X is an alkylene group having 3 or 4 carbon atoms or R_2 is -WB wherein W is an alkylene group having 1, 2, 3, 4 or 5 carbon atoms and B is (a) a pyridyl, piperidyl, pyrrolidinyl, piperazinyl or imidazolyl group optionally substituted where appropriate on the nitrogen atom with a methyl group or (b) a benzimidazolyl group optionally substituted on the benzene ring with halogen.

More preferably R_2 is $-(CH_2)_3NMe_2$ or $-(CH_2)_4NMe_2$.

Typically, Z_1 and Z_2 are the same or different and represent aryl, heteroaryl, 3- to 6- membered heterocyyl, hydrogen, C_1-C_4 alkyl, -(C_1-C_4 alkyl)-aryl, -(C_1-C_4 alkyl)-heteroaryl or -(C_1-C_4 alkyl)-(3- to 6- membered heterocyclyl), or Z_1 and Z_2, together with the N atom to which they are attached, form a said 5- or 6- membered N-containing heterocyclic group.

When Z_1 and/or Z_2 is an aryl group or a -(C_1-C_4 alkyl)-aryl group, the aryl group or moiety is typically a phenyl group or moiety or a phenyl group or moiety fused to a heteroaryl group such as a pyrrole or thiadiazole group or to a 3- to 6- membered heterocyclic group, such as a 1,4-dioxolane group, a tetrahydrofuran group or a pyrrolidine group, in particular a 2,5-dioxopyrrolidine group.

Preferred substituents on the aryl group or moiety include aryl such as phenyl, heteroaryl, 3- to 6- membered heterocyclyl, halogen, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, nitro, cyano, and, when the aryl group or moiety is fused to a heterocyclyl group, oxo. Said heteroaryl and heterocyclic substituents are typically 5- or 6- membered heteroaryl or heterocyclic groups containing 1,2 or 3 heteroatoms selected from N, O and S, for example a thiadiazolyl, thiazole, imidazole, isoxazole, isothiazole, furan, pyrazole, pyrrole or thiophene group. Thiadiazole and furan substituents are preferred heteroaryl substituents.

When Z_1 and/or Z_2 is a heteroaryl group or a -(C_1-C_4alkyl)-heteroaryl group, the heteroaryl group or moiety is typically a pyridyl, thiazolyl, thienyl or imidazolyl group or moiety or a pyridyl, thiazolyl, thienyl or imidazolyl group or moiety fused to a phenyl or cyclohexyl group.

Preferred substituents on the heteroaryl group or moiety include aryl such as phenyl, heteroaryl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl, halogen, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, nitro, cyano, and, when the heteroaryl group or moiety is fused to a heterocyclyl or carbocyclyl group, oxo.

Preferably, Z_1 is H, C_1-C_4 alkyl, for example methyl or i-propyl or phenyl and Z_2 is H, C_1-C_4 alkyl, such as methyl or i-propyl, aryl, for example phenyl, heteroaryl, for example quinoline, -(C_1-C_4 alkyl)-aryl, such as benzyl or -(C_1-C_4 alkyl)-

heteroaryl, or Z_1 and Z_2 together form a said heterocyclic group.

Preferably R_3 is hydrogen, C_1-C_4 alkyl, aryl or -(C_1-C_4 alkyl)-aryl. More preferably, R_3 is hydrogen, phenyl or benzyl, most preferably hydrogen.

Preferably R_4 is -CO_2A' wherein A' is as defined above, -$CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined above, C_1-C_4 alkyl, -CF_3, -CCl_3, halogen, C_1-C_4 alkoxy, aryl, for example phenyl, heteroaryl, for example oxadiazolyl, furanyl or pyridyl, -(C_1-C_4 alkyl)-aryl such as benzyl or -(C_1-C_4 alkyl)-heteroaryl. More preferably R_4 is -CO_2H, -CO_2Me, phenyl, oxadiazolyl, furanyl, pyridyl, C_1-C_4 alkyl, -(C_1-C_2 alkyl)-phenyl or -$CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined above.

Preferred compounds of the invention are compounds of formula (Ia) or (Ib), as defined above, in which:

- Y is -O-;

- R_1 is hydrogen; aryl for example phenyl, heteroaryl, -(linear C_1-C_4 alkyl)-R in which the alkyl moiety is unsubstituted at the α position and R is aryl, for example phenyl, or heteroaryl, for example imidazolyl or thienyl, or R_1 is linear C_1-C_4 alkyl optionally substituted other than at the α position with hydroxy, halogen, -CF_3, -CCl_3, -NA'_2, -CO_2A' or -NH-CO-(C_1-C_4 alkyl); or R_1 is -$CONA'_2$; -COA" or -$SO_2A"$; wherein A' and A" are as defined above;

- R_2 is -$XNMe_2$ wherein X is an alkylene group having 3 or 4 carbon atoms or R_2 is -WB wherein W is an alkylene group having 1, 2, 3, 4 or 5 carbon atoms and B is (a) a pyridyl, piperidyl, pyrrolidinyl, piperazinyl or imidazolyl group optionally substituted where appropriate on the nitrogen atom with a methyl group or (b) a benzimidazolyl group optionally substituted on the benzene ring with halogen;

- R_3 is hydrogen, C_1-C_4 alkyl, aryl or -(C_1-C_4 alkyl)-aryl; and

- R_4 is -CO_2A' wherein A' is as defined above, -$CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined above, C_1-C_4 alkyl, -CF_3, -CCl_3, halogen, C_1-C_4 alkoxy, aryl, for example phenyl, heteroaryl, for example oxadiazolyl, furanyl or pyridyl, -(C_1-C_4 alkyl)-aryl such as benzyl, or (C_1-C_4 alkyl)-heteroaryl,

and pharmaceutically acceptable salts thereof.

Further preferred compounds of the invention are compounds of formula (Ia) or (Ib), as defined above, in which:

- Y is -O-;

- R_1 is hydrogen, -(CH_2)-aryl for example benzyl, -(CH_2)-heteroaryl for example -CH_2-imidazolyl or -CH_2-thienyl, aryl for example phenyl, 3-hydroxy-n-propyl, 3-dimethylamino-n-propyl, 2-phenylethyl, 2-(CO_2Me)-ethyl, -$CONMe_2$, -COMe, -COPh or -SO_2Me;
- R_2 is -$(CH_2)_3NMe_2$ or -$(CH_2)_4NMe_2$;
- R_3 is hydrogen, phenyl or benzyl; and
- R_4 is -CO_2H, -CO_2Me, phenyl, oxadiazolyl, furanyl, pyridyl, -C_1-C_4 alkyl, -(C_1-C_2 alkyl)-phenyl or -$CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined above,

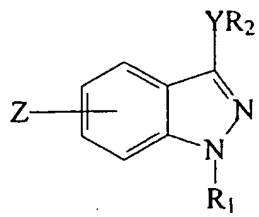
and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (Ib) are those in which Y is -O-, R_1 is aryl or -(C_1-C_4 alkyl)-R wherein R is aryl or heteroaryl, R_2 is -$XNMe_2$ or -XNHMe wherein X is as defined above, R_3 is hydrogen and R_4 is aryl, for example phenyl, or -(C_1-C_4 alkyl)-aryl, for example benzyl, and pharmaceutically acceptable salts thereof. When R in the formula (Ib) is -(C_1-C_4 alkyl)-R, R is typically phenyl, phenyl fused to 1,4-dioxolane or thienyl.

The above preferred substituents may be substituted or unsubstituted as set out above.

In a further preferred embodiment of the invention, R_3 and R_4 form the divalent group -$(CH)_4$-. This group is optionally substituted, i.e. each hydrogen atom in the group can be replaced by a suitable substituent. Suitable substituents include one or more, preferably one or two, substituents selected from aryl such as phenyl, heteroaryl, -(C_1-C_4 alkyl)-R wherein R is aryl or heteroaryl, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 haloalkyl, halogen such as chlorine, hydroxy, nitro, cyano, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, -NA'_2, -CO_2A' and -NH-CO-A' wherein A' is as defined above. Preferred substituents include methyl, ethyl, hydroxy, chlorine, methoxy, dimethylamino and -NH-acetyl.

Further preferred compounds of the invention are compounds of formula (Ia), or pharmaceutically acceptable salts thereof in which R_3 and R_4 together form the said divalent group -$(CH)_4$-. These compounds are indazoles and have the formula (Ic) as set out below.



(Ic)

in which Y, R_1 and R_2 are as defined above and Z denotes one or more, preferably one or two, selected from hydrogen, aryl such as phenyl, heteroaryl, -(C_1-C_4 alkyl)-R wherein R is aryl or heteroaryl, C_1-C_4 alkyl such as methyl or ethyl, C_1-C_4 haloalkyl, halogen such as chlorine, hydroxy, nitro, cyano, C_1-C_4 alkoxy such as methoxy or ethoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, -NA'$_2$, -CO_2A' and -NH-CO-A' wherein A' is as defined above. Preferably, Z is one or two selected from hydrogen, methyl, ethyl, hydroxy, chlorine, dimethylamino or -NH-acetyl.

Typically, R_2 in the formula (Ic) is -XNMe$_2$ or -XNHMe wherein X is defined above or -WB wherein W and B are as defined above.

Preferred compounds of formula (Ic) are those in which Y is -O-, R_1 is hydrogen, aryl, for example phenyl, heteroaryl, -(linear C_1-C_4 alkyl)-R in which the alkyl moiety is unsubstituted at the α position and R is aryl, for example phenyl, or heteroaryl, for example imidazolyl or thienyl, or R_1 is linear C_1-C_4 alkyl optionally substituted other than at the α position with hydroxy, halogen, -CF_3, -CCl_3, -NA'$_2$, -CO_2A' or -NH-CO-(C_1-C_4 alkyl) or R_1 is -CONA'$_2$, -COA" or -SO_2A" wherein A' and A" are as defined above, and R_2 is -XNMe$_2$ wherein X is an alkylene group having 3 or 4 carbon atoms or R_2 is -WB wherein W is an alkylene group having 1, 2, 3, 4 or 5 carbon atoms and B is (a) a pyridyl, piperidyl, pyrrolidinyl, piperazinyl or imidazolyl group optionally substituted where appropriate on the nitrogen atom with a methyl group or (b) a benzimidazolyl group optionally substituted on the benzene ring with halogen, or pharmaceutically acceptable salts thereof.

More preferred compounds of formula (Ic) are those in which Y is -O-, R_1 is hydrogen, -(CH_2)-aryl, for example benzyl, -(CH_2)-heteroaryl, for example -CH_2-imidazolyl or -CH_2-thienyl, aryl for example phenyl, 3-hydroxy-n-propyl, 3-dimethylamino-n-propyl, 2-phenylethyl, 2-(CO_2Me)-ethyl, -CONMe$_2$, -COMe, -COPh or -SO_2Me and R_2 is -$(CH_2)_3$ NMe$_2$ or -$(CH_2)_4$ NMe$_2$, or pharmaceutically

acceptable salts thereof.

The present invention includes pharmaceutically acceptable salts of the compounds of the invention. Suitable salts include salts with pharmaceutically acceptable acids, both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succininc, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Salts may also be formed with pharmaceutically acceptable bases such as alkali metal (eg sodium or potassium) and alkali earth metal (eg calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of the invention are :

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole-5-carboxylic acid;

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-methylaminocarbonyl-1*H*-pyrazole;

3-(3-Dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole;

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-dipropylaminocarbonyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(N-morpholinocarbonyl)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-trifluoromethyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(dimethylaminocarbonyl)-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(benzylaminocarbonyl)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-pyrazole

3-(2-(1-Methyl-2-pyrrolidinyl)ethyloxy)-5-phenyl-1*H*-pyrazole

3-(1-Methyl-3-piperidinyl)methyloxy-5-phenyl-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-4-phenyl-1*H*-pyrazole

1-Benzyl-3-(5-hydroxymethyl-2-furyl)methyloxy-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-indazole

1-Benzyl-3-(4-dimethylaminobutyloxy)-1*H*-indazole

1-Acetyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole
3-(3-Dimethylaminopropyloxy)-1-(3-hydroxypropyl)-1*H*-indazole
1-Benzoyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole
3-(3-Dimethylaminopropyloxy)-1*H*-indazole
3-(3-Dimethylaminopropyloxy)-1-(2-phenylethyl)-1*H*-indazole
(3-Dimethylaminopropyloxy)-1-methylsulfonyl-3-1*H*-indazole.
1-(3-Dimethylaminopropyl)-3-(3-dimethylaminopropyloxy)-1*H*-indazole
3-(3-Dimethylaminopropyloxy)-1-(2-methoxycarbonylethyl)-1*H*-indazole
1-Benzyl-(3-dimethylaminopropyloxy)-4-methyl-1*H*-indazole
1-Benzyl-(3-dimethylaminopropyloxy)-6-methyl-1*H*-indazole
1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole
1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole
1-Benzyl-5-(3-dimethylaminopropyloxy)-3-phenyl-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-1-methyl-1*H*-indazole
5-Phenyl-3-(4-pyridinylmethyloxy)-1*H*-pyrazole
3-(4-Dimethylaminobutyl)-5-phenyl-1*H*-pyrazole
3-(3-Dimethylaminopropylamino)-5-phenyl-1*H*-pyrazole
1-Benzyl-3-(5-dimethylaminopentyloxy)-1*H*-indazole
1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-methyl-1,2,4-oxadiazol-5-yl]-1*H*-pyrazole
1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-phenyl-1,2,4-oxadiazol-5-yl]-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-5-(3-furyl)-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-5-(4-pyridyl)-1*H*-pyrazole
1,5-Diphenyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-4-benzyl-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-5-benzyl-1*H*-pyrazole
3-(3-Dimethylaminopropyloxy)-5-ethoxycarbonylethyl-1*H*-pyrazole
3-(3′-Dimethylamino-1′-propoxy)-5-(3′,4′,5′-trimethoxyphenyl)-1*H*-pyrazole
5-Phenyl-3-(3-pyrrolidin-1-yl)-propyloxy)-1*H*-pyrazole
3-(3-Dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid methyl ester
1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-

methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-5-hydroxymethyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,4,5-trimethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-dimethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-chloro-4-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-indol-5-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid thiazol-2-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-trifluoromethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-difluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-benzoimidazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1-phenyl-1*H*-pyrazol-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4,5,6,7-tetrahydro-benzothiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-[1,2,3]thiadiazol-4-yl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-oxazol-5-yl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-phenyl-thiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-5-trifluoromethyl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid benzo [1,2,5]thiadiazol-4-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-2-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-4-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2,4-trimethyl-2,3-dihydro-benzofuran-7-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide

1,5-Dibenzyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Trifluoromethyl-4′-fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-(Trifluoromethoxy)benzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(2′-Fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(2′-Chlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Nitrobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Phenylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-Piperonyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-([1-(4′-Chlorobenzyl)-1*H*-imidazol-2-yl]methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(2′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(2′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Methylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

and pharmaceutically acceptable salts thereof.

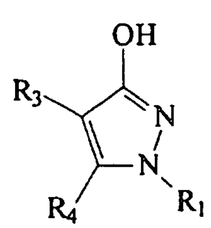
Certain compounds of the invention are novel. Thus, the present invention also provides a compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in which R_1 to R_4 are as defined above except for:

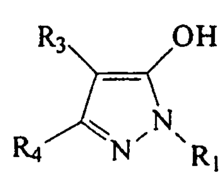
(a) compounds of formula (Ia), in which Y is -O-, R_3 and R_4 together form a benzene ring optionally substituted with a chlorine atom, an amino group, a methoxy group or a nitro group, R_2 is $-XNMe_2$ wherein X is ethylene or propylene and R_1 is C_1-C_4 alkyl, phenyl, benzyl or 2-phenylethyl;

(b) compounds of formula (Ia) in which Y is -O-, R_1 and R_3 are each a phenyl group optionally substituted with an alkyl group, an alkoxy group or a halogen atom, R_4 is hydrogen, and R_2 is $-XNMe_2$ or -XNHMe wherein X is ethylene or propylene or R_2 is -WB wherein W is ethylene or propylene and B is a 5- or 6- membered N- containing heterocycle, linked to the group W via the N atom; and

(c) compounds of formula (Ia) in which Y is -O-, R_3 and R_4 together form a benzene ring, R_2 is $-(CH_2)_3NMe_2$ and R_1 is hydrogen or $-(CH_2)_3NMe_2$.

The compounds of the present invention in which Y is -O- may be prepared by a process comprising reacting a compound of formula (IIa) or (IIb):


(IIa)


(IIb)

in which R_1, R_3 and R_4 are as defined above, with a compound of formula (III)

$$X\text{-}R_2 \qquad \text{(III)}$$

in which X is OH or a leaving group and R_2 is as defined above, and optionally salifying the thus obtained compound of formula (I).

When X is OH, the reaction proceeds via a Mitsunobu reaction. Typically, this reaction takes place in the presence of an azodicarboxylate coupling agent such as 1,1'-(azodicarbonyl)dipiperidine or 1,1-azobisdimethylformamide and a trialkylphosphine such as tri-n-butylphosphine. The reaction typically takes place in a hydrocarbon solvent such as toluene or tetrahydrofuran at a temperature of from 0 to 100°C, preferably from 20 to 80°C.

When X is a leaving group, it is preferably a halide such as a chloride, bromide or iodide. When X is a leaving group, the reaction proceeds via nucleophilic attack on the compound of formula (III). Typically, the reaction takes place in the presence of a base in a solvent such as tetrahydrofuran at a temperature of from 0 to 100°C. When R_3 and R_4 together form an optionally substituted $-(CH)_4-$ group, the base is typically sodium hydride. When R_3 and R_4 do not form a $-(CH)_4-$ group, the base is typically potassium tertiary butoxide or potassium carbonate.

A compound of formula (Ia) or (Ib) in which R_1 is a hydrogen atom may be converted into another compound of formula (Ia) or (Ib) by a reaction with a compound of formula:

$$X\text{-}R_1$$

wherein R_1 is as defined above with the exception of a hydrogen atom or an aryl group and X is OH or a leaving group. When R_1 is a linear C_1-C_4 alkyl group or a -(linear C_1-C_4 alkyl)-aryl group, X is OH or a leaving group. Under these circumstances, the reaction conditions are typically the same as for the reaction between the compounds of formulae (II) and (III). When R_1 is $-CONA'_2$, -COA" or $-SO_2A"$ wherein A' and A" are as defined above, X is typically a leaving group such as chlorine or bromine. The reaction typically takes place in the presence of a base in a solvent such as tetrahydrofuran at a temperature of from 0 to 100°C.

A compound of formula (Ia) or (Ib) in which R_1 is a hydrogen atom may also be converted into a compound of formula (Ia) or (Ib) in which R_1 is an aryl or heteroaryl group by reaction with a compound of formula:

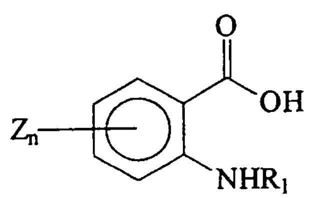
$$(OH)_2B - R_1$$

wherein R_1 is an aryl or heteroaryl group. The reaction typically takes place in the presence of cupric acetate and a base such as pyridine in a solvent such as dichloromethane and at a temperature of from 0 to 50°C.

The compounds of formulae $X\text{-}R_1$, $X\text{-}R_2$ and $(OH)_2B\text{-}R_1$ are known compounds or may be prepared by analogy with known processes.

Compounds of formula (IIa) or (IIb) in which R_3 or R_4 is hydrogen may be converted to corresponding compounds in which R_3 or R_4 is halogen by standard halogenation techniques, such as, for example, those described in "Reactions, Mechanisms and Structure", Jerry March, 3rd edition, pages 596 et seq.

Compounds of formula (IIa) in which R_3 and R_4, together with the carbon atoms to which they are attached, form an optionally substituted benzene ring, can be prepared by diazotisation of an anthranilic acid of formula (IX) followed by reduction:



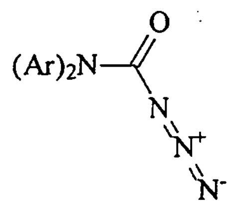
(IX)

wherein n is from 0 to 4 and Z and R_1 are as defined above. Such techniques are well known in the art and are described, for example, in Palazzo *et al*, J. Med, Chem, 9, 38, (1966) and Baiocchi *et al*, Synthesis, (1978), 633. Typically, the compound of formula (IX) is treated with a diazotisation reagent, such as sodium nitrite, in an acidic aqueous medium, such as aqueous HCl. Subsequent reduction can be effected with a reducing agent such as sodium hydrosulfite.

Compounds of formula (IX) in which R_1 is H are known in the art. Compounds of formula (IX) in which R_1 is other than H can be prepared from

compounds of formula (IX) in which R_1 is H by reacting such compounds with suitable alkyl, or -alkyl-aryl chlorides or bromides (e.g. benzyl bromide) in the presence of a base, such as sodium hydroxide, in a polar solvent such as water. Such reactions are described in Palazzo et al, *J. Med Chem.* 9, 38, (1966).

Compounds of formula (IIa) and (IIb) in which R_3 and R_4, together with the carbon atoms to which they are attached, form a benzene ring and R_1 is an aryl group can be prepared from the carbamoyl azides of formula (XI) using the methods set out in Koga et al, *Tetrahedron,* 28, 4515, (1972)

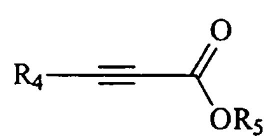


(XI)

wherein Ar is an aryl group, such as a phenyl group.

The compound of formula (XI) can be prepared from the corresponding acyl chloride by known methods.

Compounds of formula (IIa) and (IIb) in which R_3 and R_4 do not form an optionally substituted group $-(CH)_4-$ and in which R_3 is hydrogen, can be prepared by reacting an alkynoate of formula (XIX):



(XIX)

in which R_4 is as defined above and OR_5 is a leaving group, with a hydrazine of formula (XX)

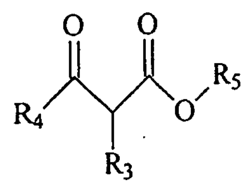
$$R_1\text{-NH-NH}_2 \quad \text{(XX)}$$

in which R_1 is as defined above.

This reaction is typically conducted in a polar solvent such as ethanol at a

temperature of from 0 to 100°C. Similar such reactions are described in Hamper et al, *J. Org. Chem.*, 57, 5680 (1992).

Alternatively, compounds of formula (IIa) or (IIb) in which R_3 and R_4 do not form an optionally substituted group -$(CH)_4$- can be prepared by reacting a compound of formula (XXI):


(XXI)

in which R_3 and R_4 are as defined above and OR_5 is a leaving group, with a hydrazine of formula (XX) as defined above.

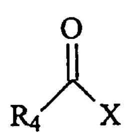
The reaction is typically conducted in a polar solvent such as ethanol at a temperature of from 0 to 100°C.

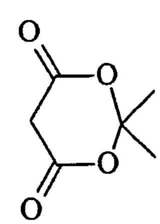
Compounds of formula (IIa) thus obtained, in which R_1 is hydrogen, can be converted into another compound of formula (IIa), in which R_1 is not hydrogen, by the methods set out above.

Typically, OR_5 is methoxy or ethoxy.

The compounds of formulae (XIX) and (XX) are known compounds or may be prepared by analogy with known processes.

The compounds of formula (XXI), in which R_3 is hydrogen, can be prepared by reaction of an acid halide of formula (XXIII) with a compound of formula (XXIV):


(XXIII)


(XXIV)

in which R_4 is as defined above and X is a halogen such as chlorine.

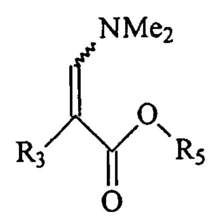
The reaction is typically conducted in two steps, the first step involving reaction of the two compounds in the presence of a base such as pyridine in an inert solvent such as CCl_4 or dichloromethane at a temperature of from 0 to 100°C. The second step typically involves treatment of the crude isolate from the first step with

an alcohol such as ethanol at a temperature of from 0 to 100°C.

Compounds of formula (XXI) in which R_3 is other than hydrogen, aryl, heteroaryl or halogen can be prepared by reaction with a compound of formula R_3-X wherein X is a leaving group such as chlorine or bromine in the presence of a base such as lithium diisopropylamide in a solvent such as tetrahydrofuran at a temperature of -78 to 0°C.

The compounds of formula (XXIII) and (XXIV) are known compounds or may be prepared by analogy with known processes.

Compounds of formula (IIa) in which in which R_3 and R_4 do not form an optionally substituted group -(CH_4)- and R_4 is hydrogen, can also be prepared by reaction of a dimethylamino acrylate of formula (XXII)

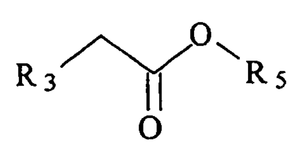


(XXII)

wherein R_3 and OR_5 are as defined above, with a hydrazine of formula (XX) as defined above. Typically, the reaction takes place in a polar solvent such as ethanol at from 0 to 100°C.

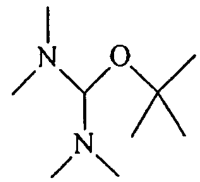
The compounds of formula (XXII) can also be used to prepare compounds of formula (XXI) as defined above, in which R_4 is hydrogen. To this end, they can be reacted with an acid, such as hydrochloric acid, in a solvent such as water at from 0 to 50°C.

The compounds of formula (XXII) can be prepared by reacting an ester of formula (XXV):



(XXV)

in which R_3 and OR_5 are as defined above, with a compound of formula (XXVI):


(XXVI)

The reaction is typically conducted in a polar aprotic solvent such as dimethylformamide at a temperature of from 0 to 150°C.

The compounds of formulae (XXV) and (XXVI) are known compounds or may be prepared by analogy with known processes.

Compounds of formula (Ia) or (Ib) in which R_2 is $-XNMe_2$ wherein X is as defined above, can be prepared from corresponding compounds having an $-XNH_2$ group at the R_2 position by reductive amination of formaldehyde, typically in the presence of a reducing agent such as sodium cyanoborohydride and in the presence of an acid such as acetic acid. The reaction is typically conducted in a solvent such as methanol at from 0 to 100°C, preferably at room temperature.

Compounds of formula (Ia) or (Ib) in which R_4 is a carboxylic acid group can be formed from an ester precursor by saponification with, for example, aqueous sodium hydroxide, using standard techniques.

Compounds of formula (Ia) and (Ib) in which R_4 is $-CONZ_1Z_2$, wherein Z_1 and Z_2 are as defined above, can be prepared from compounds of formula (I) in which R_4 is a carboxylic acid group by reaction with a compound of formula (XVIII)

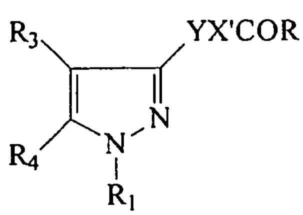
$$NHZ_1Z_2 \qquad (XVIII)$$

wherein Z_1 and Z_2 are as defined above.

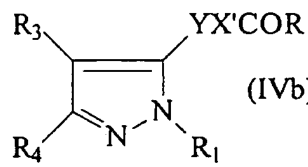
In this reaction, the compounds of formula (Ia) and (Ib) in which R_4 is a carboxylic acid group are typically treated with an activating agent such as *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethylammonium tetrafluoroborate or *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluroniumhexafluorophosphate (HATU), and are then coupled with the amines of formula (XVIII), typically in the presence of a base, such as diisopropylethylamine, in a solvent such as acetonitrile N-methyl-pyrrolidine or dimethylformamide at 0 to 100°C. The work up of compounds

thereby prepared typically involves the use of a sequestration enabling reagent, for example tetrafluorophthalic anhydride, and polymer bound scavenger resins to remove unwanted starting material. Such techniques are described in Parlow *et al*, *Tetrahedron Lett.*, 1997, **38**, 7959.

Compounds of formula (Ia) and (Ib) in which Y is $-CH_2-$ or -NH- and R_2 is $-XNMe_2$ or -XNHMe may be prepared from compounds of formula (IVa) or (IVb)



(IVa)

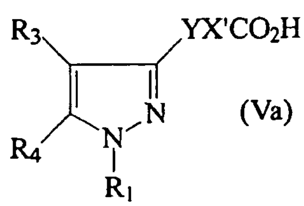


(IVb)

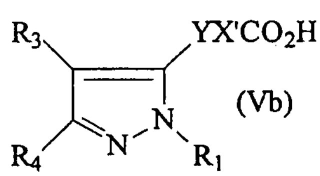
wherein R^1, R^3 and R^4 are as defined above, Y is $-CH_2-$ or -NH-, X' is an alkylene group having 2 to 4 carbon atoms and R is $-NMe_2$ or -NHMe. X' may be substituted or unsubstituted in the same way as the group X.

A compound of formula (IVa) or (IVb) is typically reacted with a hydride reducing agent in an ether solvent such as dioxane, tetrahydrofuran or diethyl ether, at a temperature of from 0 to 100°C. Preferably the reaction takes place in dioxane, with lithium aluminium hydride as the reducing agent at a temperature of from 70 to 80°C. A compound of formula (Ia) or (Ib) is thereby obtained.

Compounds of formula (IVa) or (IVb) wherein Y is a methylene (CH_2) group may be prepared from the corresponding carboxylic acid (Va) or (Vb)



(Va)



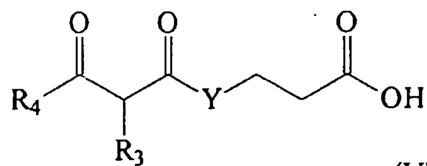
(Vb)

wherein X' is as defined above, R_1, R_3 and R_4 are as defined above and Y is $-CH_2-$.

The reaction typically takes place by preparation of an intermediate acid

chloride, followed by quenching of this intermediate with $NHMe_2$ or NH_2Me. Preferably the acid chloride is prepared by reaction with thionyl chloride and the reaction with $NHMe_2$ or NH_2Me takes place in an etheral solvent such as tetrahydrofuran or diethyl ether, at a temperature of from -50 to 50°C.

Compounds of formula (Va) and (Vb) are typically prepared from a diketone precursor of formula (VI) by reaction with a hydrazine of formula (VII) in a polar solvent such as ethanol.



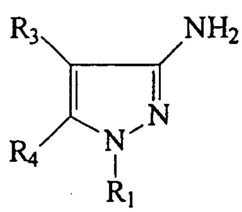
(VI)

R_1-NH-NH_2 (VII)

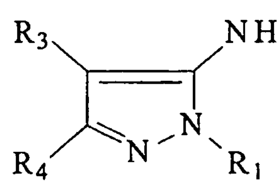
wherein R_1, R_3 and R_4 are as defined above and Y is $-CH_2-$.

Compounds of formula (VI) can be prepared by known methods, for example those set out in Wieland, D., Justus Liebigs Ann. Chem. 473, 111 (1929).

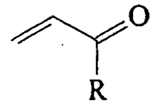
Compounds of formula (IVa) or (IVb) in which Y is -NH- can be formed by the Michael reaction of a compound of formula (VIIIa) or (VIIIb) with a suitable acrylamide (X) using the methods outlined in Kawakubo et al, *Chem. Pharm. Bull.* 35, 2292-2299 (1987).



(VIIIa)



(VIIIb)



(X)

wherein R_1, R_3 and R_4 are as described above and R is -NHMe or $-NMe_2$.

The compound of formula (X) may, if desired, be substituted on the double bond to prepare compounds of formula (IVa) and (IVb) in which the X' moiety is substituted.

Compounds of formula (VIIIa) and (VIIIb) are either commercially available or may be prepared by analogy with known processes.

The compounds of the invention are activators of sGC. They can be used as selective sGC activators. A compound of the invention can therefore be used as a vasodilator or to inhibit platelet aggregation. It can be used for the treatment or prevention of peripheral vascular diseases such as hypertension, angina pectoris, arteriosclerosis, or for the treatment or prevention of glaucoma, preeclampsia, Raynaud's Syndrome, stroke or erectile dysfunction. Conditions attributable to down regulation of sGC can thus be alleviated.

The compounds of the invention are particularly effective in the treatment or prevention of glaucoma.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, either subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginte, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for intravenous or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical daily dose is from about 0.1 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated , the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The Examples which follow illustrate the invention. The physical data of the compounds prepared are given in Table 1.

Preparation Examples

The preparation of intermediates used in synthesing the compounds of the invention is detailed below.

Preparation Example 1

N-Benzyl-anthranilic acid.

Compound prepared according to the method of Palazzo *et al. J. Med. Chem.* **1966**, *9*, 38, using anthranilic acid and benzyl bromide as starting materials. Mp 172-173 °C, lit 173 °C (Asakawa *et al. Chem. Pharm. Bull.* **1979**, *27*, 1468).

Preparation Example 2

2-(N-Benzylamino)-6-methylbenzoic acid.

Prepared according to the process of Preparation Example 1. Recrystallised from EtOH to give the title compound (46%). Mp 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.35 (m, 6H), 7.15 (t, 1H, J = 8.1 Hz), 6.51 (m, 2H), 4.47 (s, 2H), 2.58 (s, 3H). MS (EI) *m/z* 241, 106, 91.

Preparation Example 3

2-(N-Benzylamino)-4-methylbenzoic acid.

Prepared according to the process of Preparation Example 1. Recrystallised from EtOH to give the title compound (55%). Mp 156-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 8.05 (br, 1H), 7.88 (d, 1H, J = 8.5 Hz), 7.37 (m, 5H), 6.46 (m, 2H), 4.48 (s, 2H), 2.70 (s, 3H). MS (EI) 241, 106, 91.

Preparation Example 4

1-Benzyl-3-hydroxy-1*H*-indazole.

Compound prepared according to the method of Palazzo *et al*, *J. Med. Chem.* **1966**, 9, 38, using compound of Preparation Example 1 as starting material.

Preparation Example 5

1-Benzyl-3-hydroxy-4-methyl-1*H*-indazole.

Prepared from the compound of Preparation Example 2 using same process as in Preparation Example 4. Purified by flash chromatography using 20% EtOAc/cyclohexane followed by recrystallisation from MeOH/$CHCl_3$ to give the title compound (76%). Mp 182-183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.29 (m, 5H), 7.25 (dd, 1H, J = 8.5, 7.0 Hz), 7.03 (d, 1H, J = 8.5 Hz), 6.80 (d, 1H, J = 7.0 Hz), 5.25 (s, 2H), 2.70 (s, 3H). MS (EI) 238, 91.

Preparation Example 6

1-Benzyl-3-hydroxy-6-methylindazole.

Prepared from the compound of Preparation Example 3 using same process as in Preparation Example 4. Purified by flash chromatography using $CHCl_3$ followed by recrystallisation from cyclohexane/EtOAc to give the title compound (43%). Mp 195-196 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.64 (d, 1H, J = 8.1 Hz), 7.29 (m, 5H), 6.99 (s, 1H), 6.92 (d, 1H, J = 8.1 Hz), 5.22 (s, 2H), 2.45 (s, 3H). MS (EI) 238, 161, 91.

Preparation Example 7

3-Hydroxy-1-phenyl-1*H*-indazole.

Diphenyl carbamoylazide was prepared by the following method. A solution of carbamoyl chloride (10g, 43.2 mmol) in acetone (20 mL) was added dropwise to an ice-cold solution of sodium azide (4.2g, 64.6 mmol) in water (14 mL). The resultant solution was allowed to stir at room temperature (rt) overnight. The layers were separated and the aqueous layer extracted twice with ethyl acetate. The combined organic material was dried ($MgSO_4$) and concentrated under reduced pressure. A crude yield of 8.84g (86%) was obtained and no further purification was attempted.

The diphenylcarbamoylazide was then dissolved in xylene and treated as described by Koga *et al. Tetrahedron* **1972**, *28*, 4515 to give the title compound (34%) as a white solid.

Preparation Example 8

1-Benzyl-3-(5-ethoxycarbonyl-2-furyl)methyloxy-1*H*-indazole.

To 1-benzyl-3-hydroxy-1*H*-indazole the compound of Preparation Example 4 (0.5 g, 2.23 mmol) in anhydrous DMF (20 mL) was added sodium hydride (60% dispersion in mineral oil) (110 mg, 2.68 mmol) and the mixture was stirred at rt for 15 min. Ethyl 5-(chloromethyl)-2-furoate (460 mg, 2.46 mmol) in anhydrous DMF (10 mL) was added to the reaction mixture by syringe over a 30 min period. During this time the reaction mixture was heated to 100 °C and kept at this temperature for 8 h. The reaction mixture was cooled to rt and water (20 mL) was added. The mixture was extracted with diethyl ether (3 x 50 mL), combined organic extracts were dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography using cyclohexane/EtOAc (80:20) to give the title compound as a pale yellow solid (280 mg, 35%). Mp 78-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.65 (d, 1H, J = 8.1 Hz), 7.36-7.26 (m, 5H), 7.22-7.15 (m, 3H), 7.05 (t, 1H, J = 7.6 Hz), 6.57 (d, 1H, J = 3.3 Hz), 5.44 (s, 2H), 5.41 (s, 2H), 4.39 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.0 Hz). MS (EI) *m/z* 376.

Preparation Example 9

1-Benzyl-3-(4-*tert*-butoxycarbonylamino)butyloxy-1*H*-indazole.

From the compound of Preparation Example 4 and 4-bromobutylamine-*t*-butylcarbamate using same process as in Preparation Example 8. Reaction in DMF, 100 °C, 2 h, then rt overnight. The crude product was purified by flash chromatography using cyclohexane/EtOAc (70:30) to give the title compound as a white solid (480 mg, 55%). Mp 53-54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.67 (d, 1H, J = 8.1 Hz), 7.34-7.24 (m, 5H), 7.17 (d, 2H, J = 8.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 5.40 (s, 2H), 4.68 (br s, 1H), 4.41 (t, 2H, J = 6.3 Hz), 3.23 (m, 2H), 1.90 (m, 2H), 1.71 (m, 2H), 1.46 (s, 9H). MS (EI) *m/z* 395.

Preparation Example 10

Methyl 3-dimethylamino-2-phenyl acrylate.

To a solution of methyl phenylacetate (2.0 mL, 13.9 mmol) in THF (30 mL) was added *t*-butoxy-*bis*(dimethylamino)methane (3.2 mL, 15.5 mmol). The resultant solution was stirred at rt for 15 h and then the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography using 20%

EtOAc/cyclohexane followed by distillation *via* Kugelrohr to give 1.70 g (59%) of a clear, colourless oil. Bp 150 °C/~1 mmHg (oven). ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.58 (s, 1H), 7.36-7.20 (m, 5H), 3.64 (s, 3H), 2.68 (s, 6H). MS (FAB) *m/z* 206 $[MH]^+$ 205.

Preparation Example 11

3-Hydroxy-4-phenyl-1*H*-pyrazole.

A solution of intermediate the compound of Preparation Example 10 (1.0 g, 4.87 mmol) and hydrazine hydrate (0.26 mL, 5.36 mmol) in EtOH (20 mL) was heated to reflux for 5 h. The cooled solution was concentrated under reduced pressure and the solid was recrystallised from MeOH to give 0.67 g (86%) of a crystalline white solid. Mp 221.5-223 °C. ^{1}H NMR (300 MHz, DMSO-d_6) ppm 11.76 (br, 1H), 10.12 (br, 1H), 7.90 (s, 1H), 7.67 (d, 2H, J = 7.4 Hz), 7.29 (t, 2H, J = 7.7 Hz), 7.09 (t, 1H, J = 7.4 Hz). MS (EI) *m/z* 160.

Preparation Example 12

3-Hydroxy-5-trifluoromethyl-1*H*-pyrazole.

A solution of ethyl 4,4,4-trifluoro-2-butynoate (0.50 g, 3.01 mmol) and hydrazine hydrate (0.15 mL, 3.09 mmol) in EtOH (5 mL) was stirred at rt for 15 h. The solvent was removed under reduced pressure and the solid residue was purified by flash chromatography using 15% $MeOH/CHCl_3$ to give 263 mg (57%) of an off-white solid. Mp 205-208 °C. ^{1}H NMR (300 MHz, DMSO-d_6) ppm 12.84 (br, 1H), 11.25 (br, 1H), 5.67 (s, 1H) ppm. MS (EI) *m/z* 152.

Preparation Example 13

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-methoxycarbonyl-1*H*-pyrazole.

From 1-benzyl-3-hydroxy-5-methoxycarbonyl-1*H*-pyrazole (Sucrow *et al. Chem. Ber.* 1974, *107*, 1318) and 3-dimethylamino-1-propanol using same process as in Example 8.

Preparation Example 14

1-Benzyl-3-(5-*tert*-butoxycarbonylamino)pentyloxy-1*H*-indazole.

Prepared from the compound of Preparation Example 4 and 5-bromopentylamine-*t*-butylcarbamate using the same process as in Preparation Example 8. Reaction in DMF, 100°C, 3h, then rt overnight. The crude product was purified by flash chromatography using cyclohexane/EtOAc (70:30) to give the title compound as a clear oil (0.68g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.68 (d,1H, J = 8.1 Hz), 7.34-7.21 (m, 4H), 7.17 (br d, 3H, J = 8.1 Hz), 7.04 (m, 1H), 5.40 (s, 2H), 4.57 (br s, 1H), 4.39 (t, 2H, J = 6.6 Hz), 3.16 (m, 2H), 1.89 (t, 2H J = 6.8 Hz), 1.56-1.55 (m, 4H), 1.46 (s, 9H), MS (EI) *m/z* 409.

Preparation Example 15

Acetamidoxime

A solution of NaOH (1.95 g, 48.75 mmol) in water (5 mL) was added to a suspension of hydroxylamine hydrochloride (3.39 g, 48.78 mmol) in EtOH (10 mL). Acetonitrile (2.56 mL, 48.72 mmol) was then added and the reaction mixture was heated to reflux for 24 h. The EtOH was removed under reduced pressure, 2 N HCl solution (5 mL) was added and the reaction mixture heated at 100 °C, then cooled to room temperature and washed with dichloromethane (2 × 20 mL). The pH of the aqueous layer was adjusted to pH = 8 with 0.88 ammonia solution, saturated with NaCl, and then extracted with THF (4 × 50 mL). The combined THF extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a white solid. Recrystallisation from ethanol yielded the title compound as a white solid (210 mg, 6 %): mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (br s, 1H), 1.85 (s, 3H); MS (EI) *m/z* 75 $[MH]^+$.

Preparation Example 16

3-Hydroxy-5-(3-furyl)-1*H*-pyrazole

A solution of ethyl 2-oxo-3-furanpropanoate (0.50 g, 2.75 mmol) and hydrazine hydrate (0.15 mL, 3.09 mmol) in EtOH (7 mL) was heated to reflux overnight. The reaction mixture was allowed to cool to room temperature and the solid was collected. Concentration of the mother liquor provided some more solid. The combined solid was dried at 50 °C under high vacuum to give the product as a white solid (0.21 g, 50 %): mp >200 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (br,

1H), 9.49 (br, 1H), 7.99 (s, 1H), 7.70 (s, 1H), 6.79 (s, 1H), 5.67 (s, 1H); MS (FAB) *m/z* 151 $[M+H]^+$.

Preparation Example 17

3-Hydroxy-5-(4-pyridyl)-1*H*-pyrazole

Hydrazine hydrate (0.30 mL, 6.19 mmol) was added to a solution of ethyl isonicotinoylacetate (1.0 g, 5.18 mmol) in ethanol (10 mL) at room temperature. The mixture was heated to reflux overnight. The reaction mixture was allowed to cool to room temperature and then the solid was collected and recrystallised (EtOH/H_2O) to give the product as a white powder (0.73 g, 88 %): mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.44 (br, 1H), 9.81 (br, 1H), 8.58 (br s, 2H), 7.64 (d, 2H, J = 5.5 Hz), 6.14 (br s, 1H); MS (EI) *m/z* 161 $[M^+]$.

Preparation Example 18

1,5-Diphenyl-3-hydroxy-1*H*-pyrazole

A solution of KO^{t}Bu (1.0 M in THF: 41 mL, 41 mmol) was added to a mixture of phenylhydrazine (2.0 mL, 20.33 mmol) in THF (350 mL) at room temperature. The colourless solution became coloured. To this solution was added a solution of ethyl phenylpropiolate (3.40 mL, 20.59 mmol). The resultant dark red/black solution was stirred at room temperature overnight. The mixture was then heated to reflux for 4 h. The solution was allowed to cool to room temperature and then the solvent was removed under reduced pressure. The residue was dissolved in water and extracted twice with CH_2Cl_2. The aqueous layer was acidified with concentrated HCl and then the solid was collected by filtration. The crude solid was recrystallised (cyclohexane/CH_2Cl_2) to give the product as a white solid (1.75 g, 36 %): mp 251-253 °C (lit. mp 252-253 °C: *Chem. Pharm. Bull.,* 19 (7), 1389, 1971); ^{1}H NMR (300MHz, DMSO-d_6) δ 7.18-6.96 (m, 10H), 5.75 (s, 1H); MS (EI) *m/z* 236 $[M^+]$.

Preparation Example 19

3-Hydroxy-4-benzyl-1*H*-pyrazole

A solution of ethyl 2-benzyl-3-hydroxyacrylate (0.50 g, 2.42 mmol) and hydrazine hydrate (0.15 mL, 3.09 mmol) in EtOH (7 mL) was heated to reflux overnight. The

reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The solid residue was recrystallised to give the product as a cream-coloured powder (0.27 g, 64 %): mp 163-165 °C; ^{1}H NMR (300MHz, DMSO-d_6) δ 11.32 (br s, 1H), 9.38 (br s, 1H), 7.27-7.11 (m, 6H), 3.58 (s, 2H); MS (APCI+) *m/z* 175 [MH$^+$].

Preparation Example 20

3-Hydroxy-5-benzyl-1*H*-pyrazole

A solution of ethyl 3-oxo-4-phenylbutyrate (2.0 g, 9.70 mmol) and hydrazine monohydrate (0.52 mL, 10.72 mmol) in ethanol (20 mL) was heated to reflux overnight. The solution was allowed to cool to 0 °C (ice bath). The precipitate was collected and further solid was obtained from concentration of the mother liquor to give the product as a white solid (1.26 g, 75 %): mp 196-197 °C; ^{1}H NMR (300MHz, DMSO-d_6) δ 11.39 (br s, 1H), 9.34 (br s, 1H), 7.32 - 7.17 (m, 5H), 5.21 (s, 1H), 3.78 (s, 2H); MS (EI) *m/z* 174 [M$^+$].

Preparation Example 21

3-Hydroxy-5-(ethoxycarbonylethyl)-1*H*-pyrazole

A solution of diethyl 3-oxoadipate (2.0 g, 9.25 mmol) and hydrazine monohydrate (0.50 mL, 10.31 mmol) in ethanol (20 mL) was heated to reflux overnight. The solution was allowed to cool to room temperature. The precipitate was collected and unsuccessfully recrystallised (EtOH/H_2O) to give the product as a pale yellow solid (0.65 g, 38 %): ^{1}H NMR (300MHz, DMSO-d_6) δ 10.05 (br, 1H), 9.24 (br, 1H), 5.48 (s, 1H), 4.29 (q, 2H, J = 7.2 Hz), 2.94 (m, 2H), 2.81 (m, 2H), 1.41 (t, 3H, J = 7.2 Hz); MS (EI) *m/z* 184 [M$^+$].

Preparation Example 22

3-Hydroxy-5-(3′,4′,5′-trimethoxyphenyl)-1*H*-pyrazole

Ethyl-3,4,5-trimethoxybenzoyl acetate (2.0 g, 7.09 mmol) and hydrazine monohydrate (390 mg, 380 μL, 1.1 equiv.) were dissolved in EtOH (20 mL) and refluxed overnight. The reaction mixture was allowed to cool to room temperature, affording the product as a white solid which was filtered off, washed with EtOH and

dried to give 1.47 mg, 78 % of the title compound: mp 230-232 °C; ^{1}H NMR (300MHz, DMSO-d_6) δ 7.02 (s, 2H), 5.96 (s, 1H), 3.86 (s, 6H), 3.71 (s, 3H); MS (EI) *m/z* 250 [M$^+$].

Preparation Example 23

3-Pyrrolidin-1-yl-propan-1-ol

This was prepared from pyrrolidine and 3-chloro-1-propanol according to the procedure of Kolloff *et al. J. Amer. Chem. Soc.* **1948**, 70, 3862. Although, in the work up ethyl acetate was used in preference to benzene.

Preparation Example 24

3-Hydroxy-1*H*-pyrazole-5-carboxylic acid methyl ester

To hydrazine hydrate (5.01 g, 0.1 mol) in ethanol (140 mL) at room temperature was added dimethylacetylene dicarboxylate (14.2 g, 12.3 mL, 0.1 mol) dropwise. After 1h the product crystallised out. The reaction mixture was left overnight and the product filtered off 6.48 g on standing a second crop was obtained 2.3 g (64% in total): mp 235-238 °C; ^{1}H NMR (300MHz, MeOH-d_4) δ 3.85 (s, 3H), 6.02 (s, 1H); MS (EI) *m/z* 143 [MH]$^+$.

EXAMPLES

The synthesis of some of the compounds of the invention is detailed below.

Example 1

1-Benzyl-(3-dimethylaminopropyloxy)-4-methyl-1*H*-indazole.

From the compound of Preparation Example 5 and the HCl salt of 3-dimethylaminopropyl chloride using same process as in Preparation Example 8. Reaction in DMF, 80 °C, 2 h. The crude compound was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (0.5:5:94.5) to give a clear oil.

Example 2

1-Benzyl-(3-dimethylaminopropyloxy)-6-methyl-1*H*-indazole.

From the compound of Preparation Example 6 and the HCl salt of 3-dimethylaminopropyl chloride using same process as in Preparation Example 8. Reaction in DMF, 80 °C, 4 h. The crude compound was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (0.5:5:94.5) to give a solid.

Example 3

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-indazole.

From the compound of Preparation Example 7 and 3-dimethylaminopropyl chloride hydrochloride using same process as in Preparation Example 8. Reaction in DMF, 100 °C, 2 h. The crude product was purified by recrystallisation from H_2O/EtOH to give the title compound as white crystals.

Example 4

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole.

From the HCl salt of 3-dimethylaminopropyl chloride and 1-benzyl-3-hydroxy-1*H*-pyrazole (Sucrow *et al. Chem. Ber.* **1974**, *107*, 1318) as starting material, using the same process as in Preparation Example 8.

<u>Example 5</u>

1-Benzyl-3-(5-hydroxymethyl-2-furyl)methyloxy-1*H*-indazole.

To $CaBH_4$.2THF (260 mg, 1.20 mmol) suspended in dry THF (20 mL) was added the compound of Preparation Example 8 (150 mg, 0.4 mmol) in dry THF (10 mL) dropwise by syringe. The reaction mixture was heated to reflux for 18 h then cooled to rt, poured onto brine and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 30 mL) followed by CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography using cyclohexane/EtOAc (70:30) to give a white solid which was recrystallised from cyclohexane/EtOAc.

<u>Example 6</u>

1-Benzyl-3-(4-dimethylaminobutyloxy)-1*H*-indazole.

To the compound of Preparation Example 9 (200 mg, 0.51 mmol) in diethyl ether (10 mL) was added 2 equivalents of 1M HCl in diethyl ether (1.0 mL, 1.0 mmol) and the reaction was stirred overnight at rt. Two further equivalents of 1M HCl in diethyl ether were added and the reaction mixture stirred for a further 48 h. A white solid precipitated out of solution which was filtered and washed with diethyl ether. To the crude amine (72 mg, 0.22 mmol) in MeOH (5 mL) was added $NaCNBH_3$, 1M in THF (0.32 mL, 0.32 mmol) and glacial acetic acid (0.2 mL). Formaldehyde (20 mg, 0.66 mmol) in MeOH (2 mL) was then added to the reaction and the mixture was stirred overnight at rt. The MeOH was removed under reduced pressure. Water (20 mL) was added to the residue which was subsequently washed with EtOAc (2 x 10 mL), then saturated with sodium carbonate and extracted again with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a pale yellow oil.

<u>Example 7</u>

1-Benzyl-3-(5-dimethylaminopentyloxy)-1*H*-indazole.

From the compound of Preparation Example 14 and following the procedure of Example 6. 50% TFA in dichloromethane at rt for 1 h used in place of 1M HCl in

diethyl ether to give a yellow oil.

Example 8

3-(3-Dimethylaminopropyloxy)-1*H*-indazole.

To 3-indazolinone (10.0 g, 74.6 mmol), 3-dimethylamino-1-propanol (9.0 mL, 76.1 mmol), and tributylphosphine (18.5 mL, 75.0 mmol) in toluene (600 mL) was added 1,1'-(azodicarbonyl) dipiperidine (19.0 g, 75.3 mmol) portionwise. The resultant mixture was heated at 80 °C for 15 h. The cooled mixture was filtered and the residue washed with toluene. The combined filtrate was washed with three 100 mL portions of 10% aq HCl and the combined acidic washings were basified by addition of 10% aq NaOH. The basified material was extracted with CH_2Cl_2 and the combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was flash chromatographed using 0.88 ammonia/EtOH/EtOAc (2:10:88) to give the title compound, which was recrystallised from MeOH/CH_2Cl_2/petroleum ether.

Example 9

3-(3-Dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole.

From 3-hydroxy-5-phenyl-1*H*-pyrazole (Curtius *J. Prakt. Chem.* **1926**, *112*, 320) as the starting material. Using same process as in Example 8. Purification by flash chromatography using 0.88 ammonia/EtOH/EtOAc (2:10:88).

Example 10

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-pyrazole.

From 1-phenyl-3-hydroxy-1*H*-pyrazole (Harries *et al. Ber.* **1896**, *29*, 513) as the starting material, using same process as in Example 8. The work up employed involved the addition of MeOH (20 mL) and DOWEX 50W X8 (4 g) to the mixture which was then swirled at rt for 1 h. The mixture was filtered and the resin washed with MeOH (50 mL). The resin was suspended in 0.88 ammonia/MeOH (15:85) (20 mL) and swirled for 30 min. Then filtered and washed with the same mixture (20 mL). The ammonia/MeOH washings were combined and concentrated under reduced pressure. The products were purified by flash chromatography using 0.88

ammonia/MeOH/$CHCl_3$ (2:10:88).

Example 11

3-(3-Dimethylaminopropyloxy)-5-trifluoromethyl-1*H*-pyrazole.

From the compound of Preparation Example 12 using same process as in Example 8. Purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94) followed by recrystallisation from hexane/CH_2Cl_2 to give a white solid.

Example 12

3-(3-Dimethylaminopropyloxy)-4-phenyl-1*H*-pyrazole.

From the compound of Preparation Example 11 using same process as in Example 8. Purified by flash chromatography using 0.88 ammonia/EtOH/EtOAc (1:10:89) and then recrystallised from hexane/CH_2Cl_2.

Example 13

3-(2-(1-Methyl-2-pyrrolidinyl)ethyloxy)-5-phenyl-1*H*-pyrazole.

From intermediate 3-hydroxy-5-phenyl-1*H*-pyrazole and 2-(2-hydroxyethyl)-1-methyl-pyrrolidine using same process as in Example 8. Reaction carried out in THF at 70 °C for 3.5 h. After a Dowex resin work-up as in Example 10, the crude compound was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94).

Example 14

3-(1-Methyl-3-piperidinyl)methyloxy-5-phenyl-1*H*-pyrazole.

From intermediate 3-hydroxy-5-phenyl-1*H*-pyrazole and 1-methyl-3-hydroxymethylpiperidine using same process as in Example 8. Reaction carried out in THF at 70 °C for 3.5 h. After a Dowex resin work-up as in Example 10, the crude compound was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94) followed by recrystallisation from cyclohexane/EtOAc.

Example 15

5-Phenyl-3-(4-pyridinylmethyloxy)-1*H*-pyrazole.

From intermediate 3-hydroxy-5-phenyl-1*H*-pyrazole and 4-pyridinemethanol using same process as in Example 8. Reaction carried out in toluene at rt for 1 h. The crude compound was purified by flash chromatography using 0.88 ammonia/EtOH/EtOAc (1:5:94) to give a white solid.

Example 16

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole and 1-benzyl-5-(3-dimethylaminopropyloxy)-3-phenyl-1*H*-pyrazole.

Benzyl alcohol (132 mg, 0.126 mL, 1.22 mmol), tributylphosphine (246 mg, 0.3 mL, 1.22 mmol) and the compound of Example 9 (300 mg, 1.22 mmol) were dissolved in toluene (10 mL) and 1,1-azobisdimethylformamide (211 mg, 1.22 mmol) added and the reaction mixture stirred overnight. Further equivalents of benzyl alcohol, tributyl phosphine and 1,1-azobisdimethylformamide were added and the reaction mixture stirred for 4 h, then MeOH (20 mL) and DOWEX 50W X8 (4 g) were added and the mixture swirled at rt for 1 h. The mixture was filtered and the resin washed with MeOH (50 mL). The resin was suspended in 0.88 ammonia/MeOH (15:85) (20 mL) and swirled for 30 min. Then filtered and washed with the same mixture (20 mL). The ammonia/MeOH washings were combined and concentrated under reduced pressure. The products were purified by flash chromatography using MeOH/$CHCl_3$ (8:92).

Example 17

3-(3-Dimethylaminopropyloxy)-1-methyl-1*H*-indazole.

From the compound of Example 8 and methanol. Purified by preparative HPLC on reverse phase using a gradient of acetonitrile/water

Example 18

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole-5-carboxylic acid.

To the compound of Preparation Example 13 (2.43 g, 7.66 mmol) in MeOH (24 mL) was added 2.5 M aq NaOH solution (4 mL, 10 mmol) and the reaction mixture

stirred at rt overnight. The MeOH was removed under reduced pressure and water (10mL) added. The solution was added to an AG1 X8 (OH^- form) ion exchange column and eluted with water (100 mL) and 0.1 M aq HCl. Fractions containing the product were concentrated under reduced pressure to give the title compound.

__Example 19__

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-methylaminocarbonyl-1*H*-pyrazole.

To the compound of Example 18 (1 M solution in DMF, 0.5 mL, 0.5 mmol), 40% aq methylamine (0.5 mL) and DIPEA (2 M solution in DMF, 2 mL, 2 mmol) was added TBTU (1 M solution in DMF, 0.7 mL, 0.7 mmol) and the reaction mixture stirred at rt overnight. The DMF was removed under reduced pressure (~1 mmHg) and the residue taken up in saturated brine and made basic with 0.88 ammonia and extracted with THF. The crude THF extracts were dried (Na_2SO_4) and flash columned using 0.88 ammonia/EtOH/$CHCl_3$ (2:14:84) as solvent.

__Example 20__

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-dipropylaminocarbonyl-1*H*-pyrazole.

From the compound of Example 18, using the same process as in Exampe 19 and using dipropylamine as the amine. The reaction mixture was heated to 110 °C and the following work up was employed. The crude reaction mixture was cooled and water (1 mL) added followed by MeOH (5 mL). To the mixture was added DOWEX 50W X8 ion exchange resin (3 g) and the mixture stirred for 30 min, then filtered and washed with MeOH/H_2O (90:10) (10 mL). The product was eluted from the resin with MeOH/0.88 ammonia (70:30) (10 mL). Fractions containing product were concentrated under reduced pressure and flash columned using 0.88 ammonia/MeOH/$CHCl_3$ (2:10:88) as solvent.

__Example 21__

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(N-morpholinocarbonyl)-1*H*-pyrazole.

From the compound of Example 18, using same process as in Example 19 and

morpholine as the amine. The work up followed that described in Example 20.

Example 22

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(dimethylaminocarbonyl)-1*H*-pyrazole.

From the compound of Example 18, using same process as in Example 19 with dimethylamine as the amine using NMP as solvent at 100 °C. Purification by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94).

Example 23

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(benzylaminocarbonyl)-1*H*-pyrazole.

From the compound of Example 18, using same process as in Example 19 and benzylamine as the amine using NMP as solvent at 100 °C. Purification by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94).

Example 24

3-(3-Dimethylaminopropyloxy)-1-(2-methoxycarbonylethyl)-1*H*-indazole.

To a solution of the indazole of Example 8 (185 mg, 0.84 mmol) in THF (3.5 mL) was added *t*-BuOK (142 mg, 1.27 mmol) followed by methyl bromopropionate (0.11 mL, 1.00 mmol). The resultant mixture was heated to reflux for 4 h, then allowed to cool and concentrated under reduced pressure. The crude material was purified by flash chromatography using 10% MeOH/$CHCl_3$.

Example 25

3-(3-Dimethylaminopropyloxy)-1-(3-hydroxypropyl)-1*H*-indazole.

From the compound of Example 8 and 3-bromopropanol, using same process as in Example 24. Purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:5:94).

Example 26

3-(3-Dimethylaminopropyloxy)-1-(2-phenylethyl)-1*H*-indazole.

From the compound of Example 8 and 1-bromo-2-phenylethane using same process

as in Example 24. Purified by flash chromatography using 5% MeOH/$CHCl_3$.

Example 27

1-(3-Dimethylaminopropyl)-3-(3-dimethylaminopropyloxy)-1*H*-indazole.

From the compound of Example 8 and 1-chloro-3-dimethylaminopropane hydrochloride using same proces of Example 24 with 2.2 equivalents of *t*-BuOK.

Example 28

1-Acetyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole.

To a solution of the HCl salt of the compound of Example 8 (123 mg, 0.48 mmol) in dry CH_2Cl_2 (3 mL) was added acetic anhydride (0.11 mL, 1.12 mmol) and the resultant mixture was stirred at rt for 48 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:3:96).

Example 29

1-Benzoyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole.

To a solution of the HCl salt of the compound of Example 8 (182 mg, 0.71 mmol) and pyridine (0.13 mL, 1.57 mmol) in CH_2Cl_2 at −30 °C was added benzoyl chloride (0.11 mL, 0.92 mmol). The solution was allowed to warm to rt over 6 h, then it was washed twice with 1M aq NaOH, twice with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography using a 3−10% gradient of MeOH/$CHCl_3$.

Example 30

1-Methylsulfonyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole.

From the HCl salt of the compound of Example 8 and methanesulfonylchloride using the same process as in Example 29. Reaction mixture was kept at rt for 48 h then warmed to 40 °C for 5 h.

Example 31

3-(4-Dimethylaminobutyl)-5-phenyl-1*H*-pyrazole

A solution of lithium di-isopropylamide (2.0M in THF, 25 mL) in THF (50 mL) was cooled to -70°C. A solution of acetophenone (6g, 50 mmol) in THF (50 mL) was added dropwise and the mixture maintained at -70°C for 30 min.

Glutaric anhydride (3.42 g, 30 mmol) in THF (50 mL) was then added dropwise and the mixture stirred at - 70°C for 1 h then allowed to warm to rt. The resulting solution was poured into water and adjusted to pH=2 before extracting with diethyl ether and drying the organic extract over magnesium sulfate.

Filtration and evaporation provided 8 g (68%) of 7-phenyl-5,7-diketo heptanoic acid. This material (2 g, 8.5 mmol) was reacted with hydrazine hydrate (2 mL) in refluxing ethanol (20 mL). After 2 h the cooled solution was concentrated under reduced pressure to yield 5-phenyl-1*H*-pyrazole-4-butanoic acid as a crude oil (1.8 g, 92%) which solidified on standing. This compound (1.5 g, 6.5 mmol) was treated with thionyl chloride (5 mL) at 60°C for 3 h then cooled and concentrated under reduced pressure. The resulting dark oil was suspended in diethyl ether and dimethylamine (2.0M in THF, 5mL) was added with stirring.

After stirring overnight the solution was concentrated under reduced pressure and purified by flash chromatography using CH_2Cl_2/MeOH (95:5), to yield 3-(4-dimethylaminocarbonylbutyl)-5-Phenyl-1*H*-pyrazole (450 mg, 20%) as a white powder. Mp. 148°C. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 7.75 (d, 2H, J = 8 Hz), 7.45-7.25 (m, 3H), 6.40 (s, 1H), 2.95 (s, 6H), 2.80 (t, 3H, J = 6Hz), 2.45 (m, 2H), 2.05 (m, 2H), MS (APCI, $^+$ve) *m/z* 258 $[MH]^+$.

The 3-(4-Dimethylaminocarbonylbutyl)-5-Phenyl-1*H*-pyrazole thus obtained (150 mg, 0.58 mmol), was added to dioxane (20 mL) and lithium aluminium hydride (1.0M in THF, 2 mL) was added. The resulting solution was heated at 80°C for 6 hours then cooled. Dioxane moistened with water (2 mL) was added, followed by 1M sodium hydroxide (1 mL) and the mixture heated at 80°C for 45 min then cooled and filtered. The filtrate was concentrated under reduced pressure, toluene added and evaporation repeated. Purification was by flash chromatography using

$CHCl_3$/MeOH/0.88 ammonia (90:10:1).

Example 32

3-(3-Dimethylaminopropylamino)-5-phenyl-1*H*-pyrazole

A mixture of commercially available 3-amino-5-phenyl-1*H*-pyrazole (159 mg, 1 mmol) and dimethylacrylamide (120 mg, 1.2 mmol) were heated at 80°C with stirring for 2 h then allowed to cool. Purification was by flash chromatography using $CHCl_2$/MeOH (95:5), to obtain thereby 3-(3-dimethylaminocarbonylpropylamino)-5-phenyl-1*H*-pyrazole.

The title compound was prepared from 3-(3-dimethylaminocarbonylpropylamino)-5-phenyl-1*H*-pyrazole using the same process as in Example 31. Purification was by flash chromatography using $CHCl_3$/MeOH/0.88 ammonia (95:5:1). The resulting oil was converted to its hydrochloride salt with HCl (1.0 M in diethyl ether).

Example 33

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-methyl-1,2,4-oxadiazol-5-yl]-*1H*-pyrazole

Sodium hydride (0.12 g, 60%, 2.88 mmol) was added to a solution of the compound of Preparation Example 15 (0.209 g, 2.82 mmol) in dry THF (30 mL) and heated to 50 °C. A solution of 1-benzyl-3-(3-dimethylaminopropyloxy)-5-methoxycarbonyl-1*H*-pyrazole (Preparation Example 13) (0.30 g, 0.942 mmol) in dry THF (10 mL) was added and the reaction mixture was heated to reflux for 18 h. The cooled mixture was concentrated under reduced pressure and partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with a further 2 × 100 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification was by flash chromatography using $CHCl_3$/MeOH/0.88 ammonia (95:4:1).

Example 34

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-phenyl-1,2,4-oxadiazol-5-yl]-*1H*-

pyrazole

From benzamidoxime and 1-benzyl-3-(3-dimethylaminopropyloxy)-5-methoxycarbonyl-1*H*-pyrazole (Preparation Example 13) using the same process as in Example 33 except the reaction mixture was heated to reflux for 5h and purification was by flash chromatography using $CHCl_3$/MeOH/0.88 ammonia (96:3:1).

Example 35

3-(3-Dimethylaminopropyloxy)-5-(3-furyl)-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (0.45 g, 1.78 mmol) was added to a solution of 3-hydroxy-5-(3-furyl)-1*H*-pyrazole (Preparation Example 16) (0.18 g, 1.20 mmol), 3-dimethylaminopropanol (0.22 mL, 1.86 mmol) and tributylphosphine (0.45 mL, 1.82 mmol) in toluene (12 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrate was extracted three times with 10% aqueous HCl solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH solution and re-extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:10:89) to give the product as a white solid (0.11 g, 39 %) which was recrystallised (hexane/CH_2Cl_2).

Example 36

3-(3-Dimethylaminopropyloxy)-5-(4-pyridyl)-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (0.95 g, 3.77 mmol) was added to a solution of 3-hydroxy-5-(4-pyridyl)-1*H*-pyrazole (Preparation Example 17) (0.40 g, 2.48 mmol), 3-dimethylaminopropanol (0.45 mL, 3.80 mmol) and tributylphosphine (0.95 mL, 3.85 mmol) in toluene (25 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrates were extracted three times with 10% aqueous HCl

solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH solution and re-extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:10:89) to give the product as a white solid (0.39 g, 64 %) which was recrystallised (hexane/CH_2Cl_2) to produce off-white prisms.

Example 37

1,5-Diphenyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (0.32 g, 1.27 mmol) was added to a solution of 1,5-diphenyl-3-hydroxy-1*H*-pyrazole (Preparation Example 18) (0.20 g, 0.85 mmol), 3-dimethylaminopropanol (0.15 mL, 1.27 mmol) and tributylphosphine (0.32 mL, 1.30 mmol) in toluene (10 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrates were extracted three times with 10% aqueous HCl solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH solution and re-extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using 0.88 ammonia/EtOH/ethyl acetate (1:5:94) to give the product as a clear colourless oil (0.39 g, 64 %).

Example 38

3-(3-Dimethylaminopropyloxy)-4-benzyl-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (0.44 g, 1.74 mmol) was added to a solution of 3-hydroxy-4-benzyl-1*H*-pyrazole (Preparation Example 19) (0.20 g, 1.15 mmol), 3-dimethylaminopropanol (0.20 mL, 1.69 mmol) and tributylphosphine (0.43 mL, 1.74 mmol) in toluene (12 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrates were extracted three times with 10% aqueous HCl solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH

solution and re-extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:10:89) to give the product as a clear colourless oil (0.20 g, 68 %).

Example 39

3-(3-Dimethylaminopropyloxy)-5-benzyl-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (1.10 g, 4.36 mmol) was added to a solution of 3-hydroxy-5-benzyl-1*H*-pyrazole (Preparation Example 20) (0.50 g, 2.87 mmol), 3-dimethylaminopropanol (0.50 mL, 4.23 mmol) and tributylphosphine (1.05 mL, 4.26 mmol) in toluene (25 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrates were extracted three times with 10% aqueous HCl solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH solution and re-extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography 0.88 ammonia/MeOH/$CHCl_3$ (1:10:89) to give the product as a white solid which was recrystallised from hexane (yield 46 %).

Example 40

3-(3-Dimethylaminopropyloxy)-5-ethoxycarbonylethyl-1*H*-pyrazole

1,1′-(Azodicarbonyl)dipiperidine (0.75 g, 2.97 mmol) was added to a solution of 3-hydroxy-5-(ethoxycarbonylethyl)-1*H*-pyrazole (Preparation Example 21) (0.50 g, 2.71 mmol), 3-dimethylaminopropanol (0.35 mL, 2.96 mmol) and tributylphosphine (0.75 mL, 3.04 mmol) in toluene (25 mL) at room temperature. The resultant mixture was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The residue was washed with two lots of toluene and then the combined filtrates were extracted three times with 10% aqueous HCl solution. The aqueous extracts were combined, basified by the addition of 10% aqueous NaOH solution and re-extracted three times with $CHCl_3$. The $CHCl_3$ extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure.

The semi-solid residue was purified by flash chromatography using 0.88 ammonia/MeOH/$CHCl_3$ (1:10:89) to give the product as a colourless semi-solid (0.12 g, 17 %).

Example 41

3-(3′-Dimethylamino-1′-propoxy)-5-(3′,4′,5′-trimethoxyphenyl)-1*H*-pyrazole

3-Hydroxy-5-(3′,4′,5′-trimethoxyphenyl)-1*H*-pyrazole (Preparation Example 22) (500 mg, 1.90 mmol), tributylphosphine (575 mg, 700 μL, 2.84 mmol) and 3-dimethylaminopropan-1-ol (289 mg, 330 μL, 2.80 mmol) were dissolved in toluene (10 mL) under a nitrogen atmosphere. While stirring, 1,1′-(azodicarbonyl)dipiperidine (740 mg, 2.94 mmol) was added, forming a clear gel, and the reaction was heated to 90 °C overnight. The reaction was left to cool, and the reduced Mitsunobu reagent was filtered off and washed with toluene. The organic extracts were acidified with 10% aqueous solution (3 × 25 mL), and the acidic layers combined, and basified with 10% NaOH solution (100 mL). The product was then extracted from the aqueous phase with dichloromethane (3 × 50 mL) and the organic extracts combined, dried over $MgSO_4$, and concentrated under reduced pressure. The product was further purified by flash chromatography using EtOH/ethyl acetate/0.88 ammonia (10:89:1) as eluent to afford the product as a brown oil, yield 507 mg, 79 %.

Example 42

5-Phenyl-3-(3-pyrrolidin-1-yl)-propyloxy)-1*H*-pyrazole

3-Hydroxy-5-phenyl-1*H*-pyrazole (Curtis *J. Prakt. Chem.* **1926**, *112*, 320) (500 mg, 3.13 mmol), 3-pyrrolidin-1-yl-propan-1-ol (Preparation Example 23) (400 mg, 3.13 mmol) and tributylphosphine (630 mg, 0.77 mL, 3.13 mmol) were stirred in anhydrous toluene (30 mL) at room temperature under dry nitrogen. While stirring, 1,1′-(azodicarbonyl)dipiperidine (790 mg, 3.13 mmol) was added portionwise. The reaction mixture was then heated to 80 °C for 18h. The reaction was then cooled to room temperature, filtered and washed with toluene. The toluene extracts were acidified with 10% HCl (3 × 50 mL). The acidic layers were combined and basified

with 10% NaOH solution (100 mL). The product was then extracted from the aqueous phase with dichloromethane (3 × 50 mL) and the organic extracts combined, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by flash chromatography using ethyl acetate/EtOH/0.88 ammonia (94:5:1) as eluent, followed by recrystallisation from cyclohexane/ethyl acetate to give 440 mg, 52 % of the title compound as a white crystals.

__Example 43__

3-(3-Dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid methyl ester

To 3-(dimethylamino)propan-1-ol (3.10 g, 3.6 mL, 30 mmol) in THF (45 mL) was added tributylphosphine (6.06 g, 7.39 mL, 30 mmol), 3-hydroxy-1*H*-pyrazole-5-carboxylic acid methyl ester (Preparation Example 24) (4.26 g, 30 mmol) followed by 1,1′-(azodicarbonyl)dipiperidine (7.56 g, 30 mmol). The reaction was heated to 80 °C for 1h. When cooled the reduced reagent was filtered off and washed with ethyl acetate (2 × 250 mL). The combined filtrates were washed with brine, made basic with 1M 0.88 ammonia (2 × 50 mL). The product was extracted into 1M HCl (2 × 50 mL) and the combined HCl extracts washed with $CHCl_3$ (3 × 50 mL). The HCl extracts were made basic with 0.88 ammonia and re-extracted with $CHCl_3$ (3 × 50 mL) and the extracts dried over Na_2SO_4 (4.2 g). A portion (1.0 g) of the product was purified by flash chromatography using MeOH/$CHCl_3$ (10:90) to give the product 0.7 g, (43 %).

__Example 44__

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-phenyl)-amide

To 1-benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (1.51 g, 5.0 mmol), 4-methoxyaniline (0.61 g, 5.0 mmol) and DIPEA (1.29 g, 1.74 mL, 10 mmol) in THF (20 mL) was added *O*-(7azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.90 g, 5.0 mmol) and the reaction heated to 100 °C for 1 h. The reaction mixture was cooled, poured onto aq. 1 M NaOH (100 mL) and extracted with EtOAc (3 × 50 mL). The extracts were dried (Na_2SO_4) and

the product purified by flash chromatography 0.88 NH_3/MeOH/$CHCl_3$ (2:10:88) to give 1.4g (69 %). The hydrochloride salt was prepared by dissolving the free base in ether (50 mL) and adding 1 M HCl in ether solution (50 mL) at 0 °C. The reaction mixture was stirred for 1 h then filtered and the HCl salt dried *in vacuo* at 50 °C 1mm Hg.

Example 45

1-Benzyl-3-(3-dimethylamino-propoxy)-5-hydroxymethyl-1*H*-pyrazole

To a solution of 1-benzyl-3-(3-dimethylaminopropyloxy)-5-methylaminocarbonyl-1*H*-pyrazole (Example 19) (317 mg, 1.0 mmol) in THF (20 mL) at room temperature was added $CaBH_4$ in portions. The reaction mixture was heated to reflux (90 °C oil bath) overnight. Water (30 mL) was added slowly and the reaction mixture stirred for 10 min then saturated with NaCl and extracted with THF (3 × 50 mL). The extracts were dried over $MgSO_4$. The product was purified by flash chromatography using MeOH/$CHCl_3$ (90:10) to give the product as an oil 100 mg (35 %).

Examples 46 to 73

1-Benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (30 mg, 0.1 mmol) was dissolved in anhydrous acetonitrile (1 mL). The aryl amine (different for each reaction), (0.1 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (86.0 mg, 0.3 mmol, loading 3.5 mmol/g) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluoro phosphate (HATU) (38.0 mg, 0.1 mmol) were added and the whole reaction mixture was shaken under nitrogen in anhydrous acetonitrile (4 mL) and heated to 50 °C for 5 hours. After this time the reaction mixture was cooled to room temperature. The sequestration enabling reagent -tetrafluorophthalic anhydride (65.0 mg, 0.3 mmol) was then added and the reaction mixture was shaken under nitrogen for 18 hours. Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate), (610 mg, 1.96 mmol, loading 3.18 mmol/g) was then added and the reaction mixture was shaken under nitrogen for a further 48 hours. The reactions were then filtered through filter syringes into vials and washed with methanol. The solvent was removed on a vacuum concentrator and each product was weighed and analysis was carried out by

LC-MS.

This method was used to synthesis the following compounds. The molecular weight, purity and yield of the compounds synthesised is shown in Table 1.

Example No.	Compounds
46	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-4-methoxy-phenyl)-amide
47	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-fluoro-phenyl)-amide
48	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-phenyl)-amide
49	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,4,5-trimethoxy-phenyl)-amide
50	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide
51	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide
52	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide
53	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-phenyl)-amide
54	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-dimethoxy-phenyl)-amide
55	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide
56	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-amide
57	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-chloro-4-fluoro-phenyl)-amide
58	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-indol-5-yl)-amide
59	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide

60	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid thiazol-2-ylamide
61	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide
62	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-trifluoromethoxy-phenyl)-amide
63	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-methoxy-phenyl)-amide
64	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-difluoro-phenyl)-amide
65	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-benzoimidazol-2-yl)-amide
66	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1-phenyl-1*H*-pyrazol-3-yl)-amide
67	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4,5,6,7-tetrahydro-benzothiazol-2-yl)-amide
68	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-[1,2,3]thiadiazol-4-yl-phenyl)-amide
69	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-oxazol-5-yl-phenyl)-amide
70	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-phenyl-thiazol-2-yl)-amide. *
71	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-5-trifluoromethyl-phenyl)-amide. *
72	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid benzo [1,2,5]thiadiazol-4-ylamide
73	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-2-ylamide
74	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-4-yl)-amide
75	1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2,4-trimethyl-2,3-dihydro-benzofuran-7-yl)-amide

* The synthesis of these compounds differed from the general synthesis in that the 1-benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid,

the aryl amine, the PS-DIEA and the HATU were heated to 80 °C for 5 hours.

Table 1

Results for amides of Examples 46 to 75

Example	Molecular Weight	LC-MS Results % Purity	Yield (mg)	% Yield
46	442.6	80.0	31.1	70.2
47	396.12	87.5	18.9	47.7
48	412.57	89.7	19.9	48.2
49	468.21	92.9	21.7	46.3
50	457.03	92.4	10.1	22.1
51	429.18	87.2	14.7	34.3
52	484.25	98.2	21.9	45.2
53	396.12	89.9	7.5	18.9
54	438.18	92.5	22.9	52.3
55	469.65	34.5	4.4	9.4
56	461.18	61.7	7.0	15.2
57	430.57	55.0	6.3	14.6
58	417.16	66.8	9.0	21.6
59	430.57	87.7	4.5	10.5
60	385.14	82.0	2.3	6.0
61	429.18	92.0	14.0	32.6
62	463.13	88.0	7.4	16.0
63	408.16	98.0	12.1	29.7
64	414.11	69.0	5.3	12.8
65	418.15	84.9	5.1	12.2
66	444.2	68.9	22.3	50.2
67	439.25	70.4	7.5	15.77
68	462.22	80.2	18.7	40.46
69	445.18	90.0	26.2	58.85
70	461.24	54.17	7.7	16.7
71	464.12	65.7	1.5	3.23
72	436.19	47.67	8.1	18.6
73	429.18	92.99	17.3	40.3
74	458.12	43.25	7.9	17.2
75	462.25	100.0	25.8	55.8

Example 76

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-

chloro-4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (0.5 g, 1.65 mmol) was dissolved in anhydrous acetonitrile (20 mL). 3-Chloro-p-anisidine (0.26 g, 1.65 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (1.41 g, 4.95 mmol, loading 3.5 mmol/g) and O-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (0.63 g, 1.65 mmol) were added and the whole reaction mixture was stirred under nitrogen and heated to 50 °C for 8 hours. After this time the reaction mixture was cooled to room temperature. Tetrafluorophthalic anhydride (1.09 g, 4.95 mmol) was then added and the reaction mixture was stirred under nitrogen for 18 hours. Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate), (10.4 g, 0.33 mol, loading 3.18 mmol/g) was then added and the reaction mixture was stirred under nitrogen for a further 48 hours. The reaction mixture was then filtered, washed with methanol and concentrated. The resulting residue was purified by flash chromatography using ethyl acetate/ethanol/0.88 ammonia (94:5:1) to give 0.39 g, 53 % of a brown oil.

Example 77

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide

1-Benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (bis-hydrochloride salt) (1.5 g, 3.98 mmol), *N, N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (4.46 g, 15.95 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.51 g, 3.98 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 4-bromoaniline (0.69 g, 3.98 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and filtered and the residue was washed with methanol. The solvent was removed on a vacuum concentrator. The crude product was purified by flash chromatography using a gradient from 5 to 10 % MeOH (in $CHCl_3$). The product was stirred in a 50-50 mixture of dichloromethane/sodium hydroxide (1M) (25 mL) for 30 minutes. The

organic layer was separated, dried (Na_2SO_4) and removed using a vacuum concentrator to give the title compound as the free base (yield 62 %).

Example 78

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide

1-Benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (bis-hydrochloride salt) (1.5 g, 3.98 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (4.46 g, 15.95 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.51 g, 3.98 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-aminoquinoline (0.57 g, 3.98 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours to form the title compound. The workup and purification was the same as described in Example 50 and the title compound was formed as a yellow oil (yield 21 %).

Example 79

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide

1-Benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (bis-hydrochloride salt) (1.5 g, 3.98 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (4.46 g, 15.95 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.51 g, 3.98 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-amino-4-methoxybiphenyl anisidine (0.79 g, 3.98 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours to form the title compound. The workup and purification was the same as described in Example 50 to give the free base as a pale yellow oil (yield 38 %).

Example 80

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide

This was prepared using the method of Example 76 from 1-benzyl-3-(3-dimethylaminopropoxy)-1*H*-pyrazole-5-carboxylic acid (Example 18) (0.5 g, 1.65 mmol), 1-aminoisoquinoline (0.24 g, 1.65 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (1.41 g, 4.95 mmol, loading 3.5 mmol/g) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (0.63 g, 1.65 mmol). After the work-up the resulting residue was purified by flash chromatography using ethyl acetate/ethanol/0.88 ammonia (94:5:1) to give 0.26 g, 37 % of a yellow oil.

Example 81

1,5-Dibenzyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

3-(3′-Dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole (Example 39) (50 mg, 0.20 mmol) and potassium *t*-butoxide (27 mg, 0.25 mmol) were dissolved in freshly distilled THF (5 mL) under a nitrogen atmosphere and stirred for 0.5 h. While stirring, benzyl bromide (38 mg, 27 μL, 0.22 mmol) was then added, forming a white precipitate, and the reaction was heated to 60 °C for 5 h. The solvent was then removed under reduced pressure, and purification by flash chromatography using MeOH/$CHCl_3$ (7:93) as eluent afforded the product as a red oil, yield 23 mg, 34 %.

Reference Example 1

Standard Procedure for Mitsunobu N-Alkylation of 3-(3'-Dimethylamino-1'-propoxy)-5-benzyl-1*H*-pyrazole

3-(3'-Dimethylamino-1'-propoxy)-5-benzyl-1*H*-pyrazole (Example 39) (150 mg, 0.58 mmol), tributylphosphine (187 mg, 228 μL, 0.93 mmol) and the corresponding aryl alcohol (0.64 mmol) were dissolved in toluene (3 mL) under a nitrogen atmosphere. While stirring, 1-1'-azobis(*N,N*-dimethylformamide) (160 mg, 0.93 mmol) was added to the reaction forming a yellow solution and allowed to stir at room temperature overnight. MeOH (5 mL) and Dowex 50W X8 resin (3 g) was then added, and stirred for a further 3h. The resin was then filtered off, washed with

methanol, and the resin suspended in 20% piperidine/MeOH solution, and stirred for 2 h. The resin was filtered off, washed with 20% piperidine/MeOH, and the resulting organic extracts concentrated under reduced pressure. The resulting residue was purified by flash chromatography using MeOH/$CHCl_3$ (8:92) on silica gel to provide the desired products.

Example 82

2-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

Prepared according to Reference Example 1 using 3,4-dichlorobenzyl alcohol (113 mg, 0.64 mmol) to yield 51 mg, 21%.

Example 83

1-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared as in Example 82 to yield 10 mg, 4%.

Example 84

1-(4′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 4-methoxybenzyl alcohol (88 mg, 0.64 mmol) to yield 30 mg, 14 %.

Example 85

1-(3′-Trifluoromethyl-4′-fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 4-fluoro-3-(trifluoromethyl)benzyl alcohol (124 mg, 0.64 mmol) to yield 3 mg, 1 %.

Example 86

1-(3′-(Trifluoromethoxy)benzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 3-(trifluoromethoxy)benzyl alcohol (122 mg, 0.64 mmol) to yield 19 mg, 8 %.

Example 87

1-(4′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 4-bromobenzyl alcohol (119 mg, 0.64 mmol) to yield 2 mg, 1 %.

Example 88

1-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 3-bromobenzyl alcohol (119 mg, 0.64 mmol) to yield 19 mg, 8 %.

Example 89

2-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

Prepared as in Example 88 to yield 13 mg, 5 %.

Example 90

1-(2′-Fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 2-fluorobenzyl alcohol (80 mg, 0.64 mmol) to yield 35 mg, 16 %.

Example 91

1-(2′-Chlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 2-chlorobenzyl alcohol (91 mg, 0.64 mmol) to yield 32 mg, 15 %.

Example 92

1-(4′-Nitrobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 4-nitrobenzyl alcohol (97 mg, 0.64 mmol) to yield 3 mg, 1 % of the title compound.

Example 93

1-(4′-Phenylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 4-biphenylmethanol (117 mg,

0.64 mmol) to yield 49 mg, 20 %.

Example 94

2-Piperonyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

Prepared according to Reference Example 1 using piperonyl alcohol (97 mg, 0.64 mmol) to yield 51 mg, 22 %.

Example 95

1-([1-(4′-Chlorobenzyl)-1H-imidazol-2-yl]methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1H-pyrazole

Prepared according to Reference Example 1 using [1-(4-chlorobenzyl)-1H-imidazol-2-yl]methanol (141 mg, 0.64 mmol) to yield 17 mg, 6 %.

Example 96

2-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

Prepared according to Reference Example 1 using thiophene-2-methanol (73 mg, 60 μL, 0.64 mmol) to yield 19 mg, 9 %.

Example 97

1-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared as in Example 96 to yield 1 mg, 1 %.

Example 98

1-(2′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared as in Reference Example 1 using 2-methoxybenzyl alcohol to yield 22 mg, 10 %.

Example 99

1-(3′-Methylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 1 using 3-methylbenzyl alcohol (78 mg, 0.64 mmol) to yield 19 mg, 9 %.

Reference Example 2

General Procedure for N-Arylation of 3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

3-(3′-Dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole (Example 39) (150 mg, 0.58 mmol), cupric acetate (157 mg, 0.87 mmol), pyridine (92 mg, 94 μL, 1.16 mmol) and the corresponding arylboronic acid (0.64 mmol, 1.1 equiv.) were dissolved in anhydrous dichloromethane (10 mL) and stirred in a loosely capped test tube in the presence of 4Å molecular sieves (1 g) for 3 days at room temperature. MP-Carbonate resin (3.5 mmol/g, 540 mg) was added directly to the reaction vessel and stirred for an additional day. The reaction mixture was then filtered through celite and washed with methanol, and the organic filtrate concentrated under reduced pressure. The product was then isolated by flash chromatography using MeOH/$CHCl_3$ (8:92) as eluent to afford the resulting product.

Example 100

1-Phenyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-*1H*-pyrazole

Prepared according to Reference Example 2 using phenylboronic acid (71 mg, 0.58 mmol); Yield 53 mg, 27 %.

Example 101

1-(3′-Nitrophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 3-nitrobenzeneboronic acid (106 mg, 0.64 mmol); Yield 6 mg, 3 %.

Example 102

1-(4′-Chlorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-chlorobenzeneboronic acid (100 mg, 0.64 mmol); Yield 32 mg, 15%.

Example 103

1-(4′-Fluorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyraz le

Prepared according to Reference Example 2 using 4-fluorobenzeneboronic acid (89

mg, 0.64 mmol); Yield 24 mg, 12 %.

Example 104

1-(4′-Trifluoromethylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-trifluoromethylbenzeneboronic acid (121mg, 0.64 mmol); Yield 13 mg, 4 %.

Example 105

1-(4′-(Methylthio)phenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-(methylthio)benzeneboronic acid (107 mg, 0.64 mmol); Yield 18 mg, 8 %.

Example 106

1-(3′,4′-Dichlorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 3,4-dichlorobenzeneboronic acid (121 mg, 0.64 mmol); Yield 19 mg, 8 %.

Example 107

1-(4′-Acetylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-acetylbenzeneboronic acid (104 mg, 0.64 mmol); Yield 10 mg, 5 %.

Example 108

1-(4′-Trifluoromethoxyphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-(trifluoromethoxy)-benzeneboronic acid (131 mg, 0.64 mmol); Yield 26 mg, 11 %.

Example 109

1-(3′-Thiophen)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using thiophene-3-boronic acid (81 mg, 0.64 mmol); Yield 6 mg, 3 %.

__Example 110__

1-(2′,3′-Dichlorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 2,3-dichlorobenzeneboronic acid (121 mg, 0.64 mmol); Yield 7 mg, 3 %.

__Example 111__

1-(3′-Trifluoromethylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 3-trifluoromethylbenzeneboronic acid (121 mg, 0.64 mmol); Yield 33 mg, 15 %.

__Example 112__

1-(4′-Biphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 4-biphenylboronic acid (84 mg, 0.43 mmol; all other reagent quantities scaled accordingly); Yield 62 mg, 39 %.

__Example 113__

1-(3′-Methylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 3-methylbenzeneboronic acid (58 mg, 0.43 mmol); Yield 60 mg, 45 %.

__Example 114__

1-(2′-Methoxyphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 2-methoxybenzeneboronic acid (64 mg, 0.43 mmol); Yield 13mg, 9 %.

__Example 115__

1-(2′-Methylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 2-methylbenzeneboronic acid (58

mg, 0.43 mmol); Yield 44 mg, 33 %.

Example 116

1-(3′-Acetylphenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 3-acetylphenylboronic acid (70 mg, 0.43 mmol); Yield 76 mg, 52 %.

Example 117

1-(2′,5′-Dichlorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 2,5-dichlorobenzeneboronic acid (82 mg, 0.43 mmol); Yield 4 mg, 3 %.

Example 118

1-(2′-Chlorophenyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

Prepared according to Reference Example 2 using 2-chlorobenzeneboronic acid (67 mg, 0.43 mmol); Yield 7 mg, 5 %.

Physical data for some of the compounds synthesised in the Examples and Preparation Examples is given in Table 2

TABLE 2: PHYSICAL DATA

Compound of Example	^{1}H NMR δ, $CDCl_3$, 300 MHz	MS APCI (+ve)	mp	yield %
3	7.71 (m, 4H), 7.46 (m, 3H), 7.26 (m, 1H), 7.15 (m, 1H), 4.54 (t, 2H, J = 6.5 Hz), 2.53 (t, 2H, J = 7.6 Hz), 2.30 (s, 6H), 2.10 (m, 2H)	295 M^+ EI	63.5-64.5	63
8	7.69 (dt, 1H, J = 8.0, 0.9 Hz), 7.36 (ddd, 1H, J = 8.4, 6.8, 1.1 Hz), 7.30 (dt, 1H, J = 8.4, 0.9 Hz), 7.08 (ddd, 1H, J = 7.9, 6.7, 1.2 Hz), 4.47 (t, 2H, J = 6.4 Hz), 2.56 (br t, 2H, J = 7.5 Hz), 2.32 (s, 6H), 2.26-2.07 (m, 2H)	220 $[MH]^+$ FAB	175-176	33
11	5.86 (s, 1H), 4.24 (t, 2H, J = 5.9 Hz), 2.66 (t, 2H, J = 6.8 Hz), 2.44 (s, 6H), 2.06 (m, 2H)	237 M^+ EI	85.5-86.5	51
12	7.66 (m, 3H), 7.36 (m, 2H), 7.21 (m, 1H), 4.37 (t, 2H, J = 6 Hz), 2.52 (t, 2H, J = 8 Hz), 2.29 (s, 6H), 2.04 (m, 2H)	245 M^+ EI	98.5-100	78
28	8.39 (dt, 1H, J = 8.3, 1.0 Hz), 7.67 (dt, 1H, J = 7.9, 1.0 Hz), 7.55 (ddd, 1H, J = 8.3, 7.2, 1.2 Hz), 7.31 (ddd, 1H, J = 7.9, 7.3, 0.8 Hz), 4.5 (t, 2H, J = 6.5 Hz), 2.66 (s, 3H), 2.53 (br t, 2H, J = 7.4 Hz), 2.31 (s, 6H), 2.10-2.03 (m, 2H)	262 $[MH]^+$ FAB	oil	54
25	7.68 (dt, 1H, J = 8.0, 0.9 Hz), 7.38 (ddd, 1H, J = 8.3, 6.8, 1.1 Hz), 7.27 (br d, 1H, J = 7.9 Hz), 7.05 (ddd, 1H, J = 7.9, 6.9, 0.9 Hz), 4.42 (t, 2H, J = 6.5 Hz), 4.36 (br t, 2H, J = 6.2 Hz), 3.63 (br t, 2H, J = 5.8 Hz), 2.56-2.51 (m, 2H), 2.31 (s, 6H), 2.11-2.02 (m, 2H)	278 M^+	oil	80
29	8.53 (br d, 1H, J = 8.4 Hz), 8.12 (dt, 2H, J = 7.0, 1.5 Hz), 7.72 (br d, 1H, J = 7.9 Hz), 7.64-7.46 (m, 4H), 7.37 (br t, 1H, J = 7.6 Hz), 4.45 (t, 2H, J = 6.5 Hz), 2.48 (br t, 2H, J = 7.1 Hz), 2.26 (s, 6H), 2.08-1.99 (m, 2H)	324 $[MH]^+$ FAB	oil	49
26	7.66 (dt, 1H, J = 8.0, 0.9 Hz), 7.31-7.14 (m, 6H), 7.07-6.99 (m, 2H), 4.47 (t, 2H, J = 6.5 Hz), 4.40 (br t, 2H, J = 7.5 Hz), 3.14 (br t, 2H, J = 7.5 Hz), 2.58 (br t, 2H, J = 7.6 Hz), 2.34 (s, 6H), 2.15-2.06 (m, 2H)	324 $[MH]^+$	oil	32
30	7.99 (d, 1H, J = 8.5 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.56 (t, 1H, J = 7.6 Hz), 7.36 (t, 1H, J = 7.6 Hz), 4.56 (t, 2H, J = 6.5 Hz), 3.07 (s, 3H), 2.53 (t, 2H, J = 7.3 Hz), 2.31 (s, 6H), 2.13-2.01 (m, 2H)	298 $[MH]^+$	35-36	55
27	7.64 (dt, 1H, J = 7.1, 0.9 Hz), 7.31 (ddd, 1H, J = 8.5, 6.6, 1.1 Hz), 7.24 (dt, 1H, J = 8.5, 1.0 Hz), 6.98 (ddd,	305 $[MH]^+$ FAB	oil	80

	1H, J = 7.8, 6.5, 1.1 Hz), 4.41 (t, 2H, J = 6.5 Hz), 4.20 (t, 2H, J = 6.8 Hz), 2.48 (br t, 2H, J = 7.5 Hz), 2.24 (s, 6H), 2.17 (s, 6H), 2.09-1.92 (m, 4H)			
24	7.63 (dt, 1H, J = 8.0, 1.0 Hz), 7.37 (ddd, 1H, J = 8.5, 6.4, 1.3 Hz), 7.28 (dt, 1H, J = 8.3, 1.0 Hz), 7.04 (ddd, 1H, J = 8.3, 6.4, 1.0 Hz), 4.47 (t, 2H, J = 6.9 Hz), 4.41 (t, 2H, J = 6.5 Hz), 3.64 (s, 3H), 2.88 (t, 2H, J = 6.9 Hz), 2.55 (br t, 2H, J = 7.5 Hz), 2.31 (s, 6H), 2.11-2.02 (m, 2H)	306 $[MH]^+$	oil	74
5	7.67 (d, 1H, J = 8.1 Hz), 7.32-7.18 (m, 7H), 7.03 (m, 3H), 6.44 (d, 1H, J = 3.3 Hz), 6.29 (d, 1H, J = 3.3 Hz), 5.42 (s, 2H), 5.37 (s, 2H), 4.64 (s, 2H)	334 M^+ EI	87-88	60
6	7.66 (d, 1H, J = 8.1 Hz), 7.35-7.26 (m, 4H), 7.20-7.16 (m, 3H), 7.05 (m, 1H), 5.39 (s, 2H), 4.42 (t, 2H, J = 5.5 Hz), 2.85 (t, 2H, J = 7.5 Hz), 2.58 (s, 6H), 1.90 (m, 4H)	322 $[M-H]^+$ EI	oil	96
13	7.57 (m, 2H), 7.43-7.27 (m, 3H), 5.95 (s, 1H), 4.20 (m, 2H), 3.07 (m, 1H), 2.33 (s, 3H), 2.27-2.11 (m, 3H), 2.04-1.92 (m, 1H), 1.82-1.61 (m, 3H), 1.59-1.46 (m, 1H)	272 $[MH]^+$ EI	oil	25
14	7.55 (d, 2H, J = 7.0 Hz), 7.45-7.33 (m, 3H), 5.96 (s, 1H), 4.07 (dd, 1H, J = 5.9, 9.9 Hz), 4.00 (dd, 1H, J = 7.4, 9.6 Hz), 2.98 (d, 1H, J = 11.0 Hz), 2.79 (d, 1H, J = 11.0 Hz), 2.28 (s, 3H), 2.14 (m, 1H), 1.94 (td, 1H, J = 11.0, 2.9 Hz), 1.84-1.58 (m, 4H), 1.07 (m, 1H)	273 $[M+2H]^+$ EI	oil	33
15	DMSO-d_6 12.44 (s, 1H), 8.57 (d, 2H, J = 5.9 Hz), 7.69 (d, 2H, J = 7.7 Hz), 7.44 (m, 3H), 7.34 (t, 2H, J = 7.4 Hz), 6.25 (s, 1H), 5.26 (s, 2H)	251 $[MH]^+$ EI	140-142	24
Preparation Example 13	7.27 (m, 5H), 6.22 (s, 1H), 5.59 (s, 2H), 4.25 (t, 2H, J = 6 Hz), 3.84 (s, 3H), 3.15 (m, 2H), 2.76 (s, 6H), 2.34 (m, 2H)	318 $[MH]^+$	141-142	39
18	D_2O 7.29 (m, 3H), 7.12 (m, 2H), 6.32 (s, 1H), 5.56 (s, 2H), 4.14 (t, 2H, J = 6 Hz), 3.14 (m, 2H), 2.72 (s, 6H), 2.11 (m, 2H)	304 $[MH]^+$ FAB	169-174	69
19	7.28 (m, 5H), 5.93 (br s, 1H), 5.87 (s, 1H), 5.61 (s, 2H), 4.17 (t, 2H, J = 6 Hz), 2.92 (d, 3H, J = 5 Hz), 2.43 (m, 2H), 2.24 (s, 6H), 1.93 (m, 2H)	317 $[MH]^+$	oil	16
9	7.57 (m, 2H), 7.42-7.26 (m, 3H), 5.92 (s, 1H), 4.13 (t, 2H, J = 6 Hz), 2.41 (t, 2H, J = 7 Hz), 2.21 (s, 6H), 1.90 (m, 2H)	246 $[MH]^+$ FAB	70-72	49
16	7.42-7.20 (m, 8H), 7.08 (m, 2H), 5.80 (s, 1H), 5.18 (s, 2H), 4.22 (t, 2H, J = 7 Hz), 2.48 (t, 2H, J = 8 Hz),	336 $[MH]^+$		

	2.26 (s, 6H), 1.97 (m, 2H)			
20	7.26 (m, 5H), 5.71 (s, 1H), 5.28 (s, 2H), 4.19 (t, 2H, J = 6 Hz), 3.31 (t, 2H, J = 7 Hz), 3.03 (t, 2H, J = 8 Hz), 2.45 (t, 2H, J = 8 Hz), 2.26 (s, 6H), 1.95 (m, 2H), 1.52 (m, 2H), 1.34 (m, 2H), 0.89 (t, 3H, J = 7 Hz), 0.72 (t, 3H, J = 7 Hz)	387 $[MH]^+$	oil	31
21	7.32-7.19 (m, 5H), 5.70 (s, 1H), 5.32 (s, 2H), 4.21 (t, 2H, J = 6 Hz), 3.59 (m, 4H), 3.27 (m, 2H), 3.17 (m, 2H), 2.46 (t, 2H, J = 8 Hz), 2.27 (s, 6H), 1.96 (m, 2H)	373 $[MH]^+$	75-76	43
22	7.25 (m, 5H), 5.74 (s, 1H), 5.29 (s, 2H), 4.18 (t, 2H, J = 6.4 Hz), 2.96 (s, 3H), 2.76 (s, 3H), 2.45 (t, 2H, J = 8 Hz), 2.25 (s, 6H), 1.94 (m, 2H)	331 $[MH]^+$	oil	38
23	7.28 (m, 10H), 6.19 (m, 1H), 5.90 (s, 1H), 5.63 (s, 2H), 4.54 (d, 2H, J = 6 Hz), 4.17 (t, 2H, J = 6 Hz), 2.42 (t, 2H, J = 7 Hz), 2.23 (s, 6H), 1.92 (m, 2H)	393 $[MH]^+$	78-80	32
10	7.73 (d, 1H, J = 3 Hz), 7.61 (m, 2H), 7.41 (m, 3H), 7.2 (m, 1H), 5.90 (d, 1H, J = 3 Hz), 4.30 (t, 2H, J = 4.3 Hz), 2.48 (t, 2H, J = 8 Hz), 2.27 (s, 6H), 2.00 (m, 2H)	246 $[MH]^+$	oil	20
4	7.27 (m, 5H), 7.15 (d, 1H, J = 2 Hz), 5.67 (d, 2H, J = 2 Hz), 5.13 (s, 2H), 4.17 (t, 2H, J = 6 Hz), 2.46 (t, 2H, J = 8 Hz), 2.26 (s, 6H), 1.95 (m, 2H)	260 $[MH]^+$	oil	7
16	7.78 (d, 2H, J = 7 Hz), 7.43-7.21 (m, 8H), 5.88 (s, 1H), 5.22 (s, 2H), 4.14 (t, 2H, J = 6 Hz), 2.34 (t, 2H, J = 6 Hz), 2.22 (s, 6H), 1.93 (m, 2H)	336 $[MH]^+$	oil	36
1	7.26 (m, 5H), 7.17 (m, 1H), 6.97 (d, 1H, J = 8.5 Hz), 6.76 (d, 1H, J = 7.0 Hz), 5.36 (s, 2H), 4.42 (t, 2H, J = 6.3 Hz), 2.65 (s, 3H), 2.53 (t, 2H, J = 7.7 Hz), 2.29 (s, 6H), 2.04 (m, 2H)	324 $[MH]^+$	oil	34
2	7.55 (d, 1H, J = 8.5 Hz), 7.27 (m, 3H), 7.16 (m, 2H), 6.95 (s, 1H), 6.87 (d, 1H, J = 8.5 Hz), 5.36 (s, 2H), 4.42 (t, 2H, J = 6.3 Hz), 2.51 (t, 2H, J = 7.7 Hz), 2.43 (s, 3H), 2.28 (s, 6H), 2.05 (m, 2H)	323 M^+ EI	66-67	52
17	7.62 (dt, 1H, J = 8.0, 0.9 Hz), 7.39 (ddd, 1H, J = 8.2, 6.9, 1.1 Hz), 7.24 (dt, 1H, J = 8.6, 0.7 Hz), 7.07 (ddd, 1H, J = 7.8, 6.8, 0.6 Hz), 4.49 (t, 2H, J = 5.8 Hz), 3.87 (s, 3H), 3.34 (br t, 2H, J = 7.6 Hz), 2.93 (s, 6H), 2.37-2.32 (m, 2H)	234 $[MH]^+$	oil	30
32	7.75 (d, 2H, J =8Hz), 7.40-7.20 (m, 3H), 5.75 (s, 1H), 4.80 (bs, 2H), 4.10 (m, 2H), 2.20 (s, 6H), 2.15 (m, 2H), 2.05 (m, 2H)	245 $[MH]^+$	225(HCl salt)	57

31	7.75 (d, 2H, *J* =8Hz), 7.45-7.25 (m, 3H), 6.35 (s, 1H), 2.70 (t, *J* =7Hz, 2H), 2.20 (s, 6H), 1.70 (m, 2H), 1.55 (m, 2H)	244 [MH]' FAB	91-93	82
7	7.66 (d, 1H, J = 8.1Hz), 7.34-7.24 (m, 4H), 7.19-7.16 (m, 3H), 7.04 (t, 1H, J = 7.4 Hz), 5.40 (s, 2H), 4.39 (t, 2H, J = 6.3 Hz), 2.88-2.82 (m, 2H), 2.64 (s, 6H), 1.91-1.83 (m, 2H), 1.81-1.73 (m, 2H), 1.62-1.51 (m, 2H).	338 [MH]' FAB	oil	90
33	7.24 - 7.30 (m, 5H), 6.43 (s, 1H), 5.74 (s, 2H), 4.23 (t, 2H, *J* = 6.4 Hz), 2.44 - 2.49 (m, 5H), 2.26 (s, 6H), 1.92 - 2.04 (m, 2H)	(EI) 341 M^+	58-60	70
34	8.12 - 8.15 (m, 2H), 7.49 - 7.57 (m, 3H), 7.26 - 7.38 (m, 5H), 6.51 (s, 1H), 5.84 (s, 2H), 4.27 (t, 2H, *J* = 6.2 Hz), 2.59 - 2.65 (m, 2H), 2.38 (s, 6H), 2.03 - 2.12 (m, 2H)	(EI) 403 M^+	74-76	59
35	7.70 (s, 1H), 7.49 (s, 1H), 6.59 (s, 1H), 5.86 (s, 1H), 4.22 (t, 2H, *J* = 6.3 Hz), 2.47 (t, 2H, *J* = 7.4 Hz), 2.27 (s, 6H), 1.97 (m, 2H)	(EI) 235 M^+	100-101	39
36	8.76 (d, 2H, *J* = 6.1 Hz), 7.66 (d, 2H, *J* = 6.1 Hz), 6.18 (s, 1H), 4.36 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 7.2 Hz), 2.44 (s, 6H), 2.13 (t, 2H, *J* = 6.8 Hz)	(EI) M^+ 246	103-105	64
37	7.1-7.2 (m, 10H), 5.9 (s, 1H), 4.2 (t, 2H, *J* = 6.4 Hz), 2.4 (t, 2H, *J* = 7.5Hz), 2.15 (s, 6H), 1.85-1.81 (m, 2H)	(EI) M^+ 321	oil	64
38	9.09 (br s, 1H), 7.31-7.17 (m, 5H), 7.08 (s, 1H), 4.24 (t, 2H, *J* = 6.3 Hz), 3.71 (s, 2H), 2.42 (t, 2H, *J* = 7.5 Hz), 2.26 (s, 6H), 1.94 (m, 2H)	(EI) M^+ 259	oil	68
39	7.51 - 7.36 (m, 5H), 5.68 (s, 1H), 4.29 (t, 2H, *J* = 6.4 Hz), 4.08 (s, 2H), 2.59 (t, 2H, *J* = 7.5 Hz), 2.40 (s, 6H), 2.08 (quintet, 2H, *J* = 7.0 Hz)	(EI) M^+ 259	52-54	46
40	4.16 (m, 4H), 2.87 (t, 2H), 2.62 (t, 2H), 2.45 (m, 2H), 2.26 (s, 6H), 1.94 (m, 2H),1.26 (t, 3H)	(EI) M^+		17
41	6.71 (s, 2H), 5.83 (s, 1H), 4.15 (t, 2H, *J* = 6.3 Hz), 3.83 (s, 6H), 3.80 (s, 3H), 2.46 (t, 2H, *J* = 7.4 Hz), 2.25 (s, 6H), 1.92 (quintet, 2H, *J* = 6.9 Hz)	(EI) 335 M^+	oil	79
42	7.56 (d, 2H, *J* = 7.2 Hz), 7.46-7.37 (m, 3H), 5.98 (s, 1H), 4.26 (t, 2H, *J* = 6.4 Hz), 2.66 (t, 2H, *J* = 7.6 Hz), 2.57 (br s, 4H), 2.09-2.00 (m, 2H), 1.81 (t, 4H, *J* = 3.6 Hz)	(EI) 271 M^+	109-110	52
43	6.20 (s, 1H), 4.21 (t, 1H, *J* = 6.4 Hz), 3.91 (s, 3H), 2.47 (t, 2H, *J* = 7.5 Hz), 2.28 (s, 6H), 1.97 (m, 2H)	228 $[MH]^+$	oil	43
44	HCl Salt (DMSO-d_6) 10.69 (bs, 1H), 7.75 (d, 2H, *J* = 9.0 Hz), 7.43 (m, 4H), 7.31 (d, 1H, *J* = 6.8 Hz), 7.05 (d, 2H,	409 $[MH]^+$	187-189	69

	J = 9.0 Hz), 6.80 (s, 1H), 5.73 (s, 2H), 4.30 (t, 2H, J = 6.0 Hz), 3.88 (s, 3H), 3.32 (m, 2H), 2.90 (s, 3H), 2.88 (s, 3H), 2.27 (m, 2H)	FAB		
45	7.19 (m, 3 H), 7.03 (m, 2H), 5.56 (s, 1H), 5.10 (s, 2H), 4.37 (s, 2H), 4.03 (t, 2H, J = 5.8 Hz), 2.84 (m, 2H), 2.49 (s, 6H), 2.08 (m, 2H)	290 $[MH]^+$ 302	oil	35
76	8.29 (s, 1H), 7.60 (d, 1H, J = 2.6 Hz), 7.38 (dd, 1H, J = 2.6 Hz, J = 9.0 Hz), 7.30-7.23 (m, 5H), 6.85 (d, 1H, J = 8.7 Hz), 6.12 (s, 1H), 5.62 (s, 2H), 4.15 (t, 2H, J = 6.4 Hz), 3.87 (s, 3H), 2.44 (t, 2H, J = 7.3 Hz), 2.25 (s, 6H), 1.97-1.88 (m, 2H)	(EI) 442 M^+	oil	53
77	(400 MHz, acetone-d_6) 7.70 (dd, 2H, J = 1.8 Hz, J = 8.8 Hz), 7.51 (dd, 2H, J = 2.0 Hz, J = 6.9 Hz), 7.32-7.23 (m, 5H), 6.46 (s, 1H), 5.65 (s, 2H), 4.31 (t, 2H, J = 5.92 Hz), 3.56 (t, 2H, J = 7.6 Hz), 3.17 (s, 6H), 2.39-2.32 (m, 2H)	(EI) 458 $[M+1]^+$		62
78	(400 MHz, acetone-d_6) 9.02 (d, 1H, J = 2.5 Hz), 8.83 (d, 1H, J = 2.3 Hz), 8.0 (d, 1H, J = 8.4 Hz), 7.94 (d, 1H, J = 8.1 Hz), 7.68 (dt, 1H, J = 1.4 Hz, J = 7.6 Hz), 7.59 (br t, 1H, J = 7.0 Hz), 7.32-7.23 (m, 5H), 6.59 (s, 1H), 5.71 (s, 2H), 4.31 (t, 2H, J = 6.1 Hz), 3.42 (t, 2H, J = 7.5 Hz), 3.04 (s, 6H), 2.35-2.29 (m, 2H)	(APCI) 430 $[M+1]^+$		21
79	(400 MHz, DMSO-d_6) 10.01 (br s, 1H), 8.23 (br s, 1H), 7.97 (d, 2H, J = 7.6 Hz), 7.90 (d, 1H, J = 8.3 Hz), 7.82 (t, 2H, J = 7.6 Hz), 7.72-7.67 (m, 3H), 7.63 (d, 1H, J = 7.0 Hz), 7.57-7.55 (m, 3H), 7.03 (s, 1H), 5.97 (s, 2H), 4.53 (t, 2H, J = 6.0 Hz), 4.22 (s, 3H), 3.47 (m, 2H), 3.06 (s, 6H), 2.49 (m, 2H)	(EI) 484 M^+		38
80	8.60 (br d, 1H, J = 8.3 Hz), 7.70 (overlapping dt, 1H, J = 1.1 Hz, J = 7.5 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.51 (overlapping dt, 1H, J = 1.1 Hz, J = 7.7 Hz), 7.33 (br d, 1H, J = 6.4 Hz), 7.21-7.13 (m, 5H), 7.00 (d, 1H, J = 6.8 Hz), 6.50 (s, 1H), 5.81 (s, 2H), 4.13 (t, 2H, J = 6.4 Hz), 2.40 (t, 2H, J = 7.5 Hz), 2.18 (s, 6H), 1.94-1.85 (m, 2H)	(APCI) 430 $[M+1]^+$	oil	37
81	7.24 - 6.95 (m, 14H), 5.39 (s, 1H), 4.96 (s, 2H), 4.06 (t, 2H, J = 6.4 Hz), 3.71 (s, 2H), 2,41 (t, 2H, J = 7.6 Hz), 2.20 (s, 6H), 1.88 (quintet, 2H, J = 7.0 Hz)	EI 350 $[M^+]$		34
82	(DMSO-d_6) δ 7.34 - 6.77 (m, 8H), 5.38 (s, 1H), 4.94 (s, 2H), 3.82 (t, 2H, J = 6.4 Hz), 3.77 (s, 2H), 2.13 (t, 2H, J = 7.6 Hz), 1.94 (s, 6H), 1.60 (quintet, 2H, J = 7.0 Hz)			21
83	7.25 - 6.74 (m, 8H), 5.46 (s, 1H), 4.88 (s, 2H), 4.07 (t,			4

	2H, J = 6.4 Hz), 3.74 (s, 2H), 2.43 (t, 2H, J = 7.6 Hz), 2.21 (s, 6H), 1.89 (quintet, 2H, J = 7.0 Hz)			
84	7.29 - 6.75 (m, 9H), 5.52 (s, 1H), 5.03 (s, 2H),. 4.12 (t, 2H, J = 5.3 Hz), 3.82 (s, 2H), 3.71 (s, 3H), 3.32 - 3.20 (m, 2H), 2.82 (d, 6H, J = 3.8 Hz)			14
85	7.22 - 6.96 (m, 8H), 5.49 (s, 1H), 4.93 (s, 2H), 4.12 (t, 2H, J = 5.7 Hz), 3.78 (s, 2H), 3.17 (t, 2H, J = 8.1 Hz), 2.77 (s, 6H), 2.21 -2.11 (m, 2H)			1
86	7.24 - 6.76 (m, 9H), 5.44 (s, 1H), 4.96 (s, 2H), 4.07 (t, 2H, J = 6.4 Hz), 3.72 (s, 2H), 2.41 (t, 2H, J = 7.5 Hz), 2.20 (s, 6H), 1.88 (quintet, 2H, J = 7.0 Hz)	FAB+ 434 [M^+]		8
87	7.34 - 6.78 (m, 9H), 5.41 (s, 1H), 4.89 (s, 2H), 4.11 (t, 2H, J = 5.7 Hz), 3.73 (s, 2H), 3.16 (t, 2H, J = 7.5 Hz), 2.76 (s, 6H), 1.22 - 1.14 (m, 2H)			1
88	6.72 - 6.31 (m, 9H), 4.83 (s, 1H), 4.39 (s, 2H), 3.43 (t, 2H, J = 6.4 Hz), 3.22 (s, 2H), 1.75 (t, 2H, J = 7.1 Hz), 1.56 (s, 6H), 1.21 (quintet, 2H, J = 6.8 Hz)			8
89	7.30 - 6.85 (m, 9H), 5.44 (s, 1H), 4.91 (s, 2H), 4.06 (t, 2H, J = 6.2 Hz), 3.73 (s, 2H), 2.42 (t, 2H, J = 7.5 Hz), 2.20 (s, 6H), 1.88 (quintet, 2H, J = 7.2 Hz)			5
90	7.49 - 7.07 (m, 9H), 5.66 (s, 1H), 5.30 (s, 2H), 4.32 (t, 2H, J = 6.4 Hz), 4.03 (s, 2H), 2.65 (t, 2H, J = 7.5 Hz), 2.44 (s, 6H), 2.12 (quintet, 2H, J = 6.9 Hz)	FAB+ 368 [M^+]		16
91	7.31 - 6.58 (m, 9H), 5.48 (s, 1H), 5.14 (s, 2H), 4.11 (t, 2H, J = 6.4 Hz), 3.76 (s, 2H), 2.43 (t, 2H, J = 7.6 Hz), 2.22 (s, 6H), 1.60 (quintet, 2H, J = 6.9 Hz)	FAB+ 384 [M^+]		15
92	8.02 (d, 2H, J = 8.7 Hz), 7.17 - 6.99 (m, 7H), 5.50 (s, 1H), 5.03 (s, 2H), 4.07 (t, 2H, J = 6.4 Hz), 3.74 (s, 2H), 2.39 (t, 2H, J = 7.6 Hz), 2.19 (s, 6H), 1.87 (quintet, 2H, J = 7.0 Hz)			1
93	7.50 - 7.02 (m, 14H), 5.42 (s, 1H), 5.00 (s, 2H), 4.07 (t, 2H, J = 7.5 Hz), 2.19 (s, 6H), 1.88 (quintet, 2H, J = 6.6 Hz)	FAB+ 426 [M^+]		20
94	7.24 - 6.66 (m, 8H), 5.85 (s, 2H), 5.16 (s, 1H), 4.93 (s, 2H), 3.91 (t, 2H, J = 6.4 Hz), 3.80 (s, 2H), 2.24 (t, 2H, J = 7.2 Hz), 2.12 (s, 6H), 1.79 (quintet, 2H, J = 6.8 H)			22
95	7.24 - 6.74 (m, 11H), 5.27 (s, 1H), 5.26 (s, 2H), 5.03 (s, 2H), 3.95 (s, 2H), 3.89 (t, 2H, J = 6.3 Hz), 2.32 (t, 2H, J = 7.6 Hz), 2.17 (s, 6H), 1.80 (quintet, 2H, J = 7.0 Hz)	FAB+ 464 [M^+]		6
96	7.23 - 6.84 (m, 8H), 5.18 (s, 2H), 5.15 (s, 1H), 3.93 (t,			9

	2H, J = 6.2 Hz), 3.80 (s, 2H), 2.29 (t, 2H, J = 7.2 Hz), 2.14 (s, 6H), 1.82 (quintet, 2H, J = 6.8)			
97	7.25 - 6.73 (m, 8H), 5.37 (s, 1H), 5.08 (s, 2H), 4.06 (t, 2H, J = 6.4 Hz), 3.82 (s, 2H), 2.39 (t, 2H, J = 7.5 Hz), 2.18 (s, 6H), 1.86 (quintet, 2H, J = 7.0 Hz)			1
98	7.22 - 6.64 (m, 9H), 5.35 (s, 1H), 5.02 (s, 2H), 4.05 (t, 2H, J = 6.4 Hz), 3.76 (s, 4H), 2.90 (s, 3H), 2.43 (t, 2H, J = 7.6 Hz), 2.21 (s, 6H), 1.88 (quintet, 2H, J = 7.0 Hz)			10
99	7.23 - 6.76 (m, 9H), 5.39 (s, 1H), 4.93 (s, 2H), 4.06 (t, 2H, J = 6.2 Hz), 3.73 (s, 2H), 2.41 (t, 2H, J = 7.6 Hz), 2.22 (s, 3H), 2.20 (s, 6H), 1.88 (quintet, 2H, J = 7.0 Hz)			9
100	7.65 - 7.62 (m, 2H), 7.35 - 7.30 (m, 2H), 7.24 - 7.11 (m, 6H), 5.32 (s, 1H), 3.98 (t, 2H, J = 6.4 Hz), 3.87 (s, 2H), 2.29 (t, 2H, J = 7.2 Hz), 2.12 (s, 6H), 1.84 (quintet, 2H, J = 6.8 Hz)	EI 355 $[M]^+$		27 %
101	8.63 (t, 1H, J = 2.1 Hz), 8.10 (dd, 1H, J = 7.3, 1.1 Hz), 8.00 (dd, 1H, J = 8.1, 1.1 Hz), 7.51 (t, 1H, J = 8.3 Hz), 7.26 - 7.19 (m, 5H), 5.37 (s, 1H), 4.08 (t, 2H, J = 6.2 Hz), 3.88 (s, 2H), 2.47 (t, 2H, J = 7.2 Hz), 2.22 (s, 6H), 1.96 (quintet, 2H, J = 6.7 Hz)	FAB+ 381 $[M^+]$		3%
102	7.30 - 7.03 (m, 9H), 5.53 (s, 1H), 4.13 (t, 2H, J = 6.2 Hz), 3.86 (s, 2H), 2.41 (t, 2H, J = 7.5 Hz), 2.20 (s, 6H), 1.89 (quintet, 2H, J = 7.0 Hz)	FAB+ 370 $[M^+]$		15%
103	7.62 - 6.97 (m, 9H), 5.32 (s, 1H), 3.98 (t, 2H, J = 6.4 Hz), 3.86 (s, 2H), 2.90 (t, 2H, J = 7.2 Hz), 2.12 (s, 6H), 1.84 (quintet, 2H, J = 6.8 Hz)	FAB+ 354 $[M^+]$		12%
104	7.31 - 7.03 (m, 9H), 5.55 (s, 1H), 4.14 (t, 2H, J = 6.4 Hz), 3.87 (s, 2H), 2.39 (t, 2H, J = 7.4 Hz), 2.19 (s, 6H), 1.88 (quintet, 2H, J = 7.0 Hz)	FAB+ 404 $[M^+]$		4%
105	7.57 - 7.55 (m, 2H), 7.24 - 7.11 (m, 7H), 5.31 (s, 1H), 3.98 (t, 2H, J = 6.2 Hz), 3.86 (s, 2H), 2.42 (s, 3H), 2.36 (t, 2H, J = 7.2 Hz), 2.16 (s, 6H), 1.91 - 1.82 (m, 2H)	FAB+ 382 $[M^+]$		8%
106	7.85 (d, 1H, J = 2.3 Hz), 7.57 (dd, 1H, J = 8.9, 2.3 Hz), 7.37 (d, 1H, J = 8.7 Hz), 7.27 - 7.13 (m, 5H), 5.32 (s, 1H), 4.02 (t, 2H, J = 6.2 Hz), 3.85 (s, 2H), 2.34 (t, 2H, J = 7.2 Hz), 2.15 (s, 6H)	FAB+ 404 $[M^+]$		8%
107	7.94 (d, 2H, J = 8.7 Hz), 7.82 (d, 2H, J = 8.7 Hz), 7.27 - 7.13 (m, 5H), 5.35 (s, 1H), 4.04 (t, 2H, J = 6.4 Hz), 3.88 (s, 2H), 2.54 (s, 3H), 2.37 - 2.32 (m, 2H), 2.15 (s, 6H),	FAB+ 378 $[M^+]$		5%

	1.89 (quintet, 2H, J = 6.7 Hz)			
108	7.82 (d, 2H, J = 8.7 Hz), 7.58 (d, 2H, J = 8.3 Hz), 7.27 - 7.13 (m, 5H), 5.35 (s, 1H), 4.03 (t, 2H, J = 5.8 Hz), 3.87 (s, 2H), 2.55 - 2.42 (m, 2H), 2.28 (bs, 6H), 1.99 - 1.95 (m, 2H)	FAB+ 420 [M^+]		11%
109	7.42 (dd, 1H, J = 5.3, 1.1 Hz), 7.32 (dd, 1H, J = 3.2 1.1 Hz), 7.26 - 7.12 (m, 6H), 5.27 (s, 1H), 4.02 (t, 2H, J = 5.9 Hz), 2.80 - 2.50 (m, 2H), 2.48 - 2.17 (bs, 6H), 2.04 - 1.97 (m, 2H)	FAB+ 342 [M^+]		3%
110	7.49 - 7.20 (m, 8H), 5.32 (s, 1H), 3.99 (t, 2H, J = 5.7 Hz), 3.87 (s, 2H), 2.71 (t, 2H, J = 7.4 Hz), 2.44 (s, 6H)	FAB+ 404 [M^+]		3%
111	7.93 - 7.13 (m, 9H), 5.35 (s, 1H), 4.04 (t, 2H, J = 5.7 Hz), 3.87 (s, 2H), 2.76 - 2.62 (m, 2H), 2.39 (bs, 6H), 2.06 - 1.97 (m, 2H)	FAB+ 404 [M^+]		15%
112	8.07 - 7.50 (m, 14H), 5.66 (s, 1H), 4.33 (m, 2H), 4.22 (s, 2H), 2.66 (t, 2H, J = 6.8 Hz), 2.46 (s, 6H), 2.24 - 2.18 (m, 2H)	FAB+ 412 [M^+]		39%
113	7.78 - 7.42 (m, 8H), 7.28 (d, 1H, J = 7.5 Hz), 5.61 (s, 1H), 4.28 (t, 2H, J = 6.4 Hz), 4.18 (s, 2H), 2.62 (t, 2H, J = 7.2 Hz), 2.43 (s, 6H), 2.15 (quintet, 2H, J = 6.8 Hz)	FAB+ 350 [M^+]		45%
114	7.32 - 6.91 (m, 9H), 5.29 (s, 1H), 3.93 (t, 2H, J = 6.4 Hz), 3.89 (s, 2H), 3.74 (s, 3H), 2.22 (t, 2H, J = 7.4 Hz), 2.10 (s, 6H), 1.74 (quintet, 2H, J = 6.9 Hz)	FAB+ 366 [M^+]		9%
115	7.48 - 7.39 (m, 9H), 5.54 (s, 1H), 4.17 (t, 2H, J = 6.4 Hz), 4.11 (s, 2H), 2.42 (t, 2H, J = 7.1 Hz), 2.34 (s, 3H), 2.31 (s, 6H), 1.97 (quintet, 2H, J = 6.7 Hz)	FAB+ 350 [M^+]		33%
116	7.90 - 7.87 (m, 1H), 7.75 - 7.73 (m, 1H), 7.42 (t, 1H, J = 8.0 Hz), 7.24 - 7.12 (m, 5H), 5.34 (s, 1H), 4.02 (t, 2H, J = 6.4 Hz), 3.88 (s, 2H), 2.56 (s, 3H), 2.37 (t, 2H, J = 7.2 Hz), 2.15 (s, 6H), 1.88 (quintet, 2H, J = 6.8 Hz)	FAB+ 378 [M+]		52%
117	7.41 - 7.16 (m, 8H), 5.31 (s, 1H), 3.98 (t, 2H, J = 6.4 Hz), 3.87 (s, 2H), 2.30 (t, 2H, J = 7.2 Hz), 2.15 (s, 6H), 1.80 (quintet, 2H, J = 6.8 Hz)	FAB+ 404 [M^+]		3%
118	7.44 - 7.14 (m, 9H), 5.31 (s, 1H), 3.96 (t, 2H, J = 6.4 Hz), 3.88 (s, 2H, J = 7.2 Hz), 2.11 (s, 6H), 1.77 (quintet, 2H, J = 6.8 Hz)	FAB+ 370 [M^+]		5%

Activity Example 1

Compounds of the invention were assayed to determine their ability to activate sGC. The assay employed was an enzyme immunoassay to measure changes in cGMP. To perform the assay recombinant soluble Guanylate cyclase was added to 1.1 mg/ml IBMX, 2.6 mg/ml GTP, 667 nM DeaNO and the test compound (10μM). The mixture was then incubated at room temperature for 10 minutes. Compounds were formulated in DMSO diluted in Tris HCl (pH 7.4) buffer and with a final DMSO concentration of <0.5%.

To determine the amount of cGMP produced, the Biotrak™ cGMP enzyme immunoassay system commercially available from Amersham™ was used.

The assay is based on the competition between unlabelled cGMP and a fixed quantity of peroxidase labelled cGMP for a limited amount of cGMP specific antibody. The peroxidase ligand that is bound to the antibody is immobilised on precoated microtitre wells. The amount of labelled cGMP is determind using a one pot stabilised substrate. The concentration of unlabelled cGMP in a sample is determined by interpolation from a standard curve.

The results are shown in Tables 3 and 4.

Activity Example 2

The ability of the compounds of the inventions to inhibit platelet aggregation was also determined. IC_{50} values were measured as set out below.

Materials

Prostacyclin (PGI_2 ; ICN Pharmaceuticals, Oxford) in Tris (0.05M, pH 9), Sodium citrate solution, Tyrodes solution without calcium (140mM NaCl; 3mM KCl; 12mM $NaHCO_3$; 0.4mM $NaH_2PO_4.H_2O$; 2mM $MgCl_2.6H_2O$; 0.1% Glucose) contains 0.05M Hepes, pH7.4. Collagen (collagenreagent Horm, Nycomed Arzneimittel GmbH, Munchen).

PGI_2 dissolved in Tris buffer (0.05M, pH9). Test compounds dissolved in DMSO (at 10mM) and subsequent dilutions made in Tyrodes; final assay concentration of DMSO did not exceed 0.1% (which is without effect on platelet reactivity).

Platelet Preparation

Platelets prepared according to Vagas, J.R., Radomski, M. and Moncada, S. *The use of prostacyclin in the separation from plasma and washing of human platelets.* PROSTAGLANDINS 1982; 23:6:929-945.

Briefly, fresh human blood was collected into tubes containing 1:9 sodium citrate (3.15%) and centrifuged immediately at 260g for 20 minutes to separate the red cells from the platelet rich plasma (PRP). The PRP was decanted and PGI_2 (0.3μg/ml) was added. The PRP was then centrifuged at 180g for 10mins to sediment the remaining red and white cells. The resulting PRP was decanted into new tubes, PGI_2 (0.15μg/ml) added and centrifuged at 950 g for 10 mins to sediment the platelets. The resultant platelet poor plasma (PPP) was discarded and the platelet pellet was resuspended in an equal volume of Tyrodes buffer by gently pipetting up and down. The suspension was centrifuged at 870 g for 10mins at 4 °C. The supernatant was discarded and the platelet pellet was resuspended in an equal volume of Tyrodes buffer as before. The platelets were counted (using a Coulter Counter model T540 (address)) and normalised to 250,000cells/μl using Tyrodes. The resultant suspension was placed on ice for approximately 1 hour until use.

Platelet Assays

Platelet aggregation was monitored using either a Chrono-Log model 560-CA dual channel ormodel 570-4S four channel aggregometer (Chrono-Log Corp., Havertown, PA). Aggregation was analysed by using 0.5 mL aliquots of the platelet suspension at 37 °C using % light transmittance.

For each sample, baseline reading was established for a 3 min period, followed by addition of test compound or buffer. An EC_{50} dose of collagen was added 1 min later and the response measured 3 min after addition of collagen.

Data Analysis

The amplitude of each aggregatory response, normalised to the collagen control, was used to plot dose-response curves. The concentration of drug that

inhibited collagen-induced platelet aggregation by 50% (IC_{50}) was calculated from the dose-response curves.

The results are shown in Table 4.

TABLE 3

Compound	cGMP Change with 1 μM cpd (NO Donor Present), % of DEANO response
YC-1	120 (288.40)*
Benzydamine	237
Example 18	159.04 (163)*
Example 19	147.84 (163)*
Example 9	499.08(500)*
Example 16	499.08(500)*
Example 20	292.44(240.52)*
Example 21	213.07(240.52)*
Example 11	238.97(145.61)*
Example 22	262.90(178.10)*
Example 23	276.01(178.10)*
Example 10	229.14(312.29)*
Example 13	160.24(312.29)*
Example 14	181.34(312.29)*
Example 5	110.93(146)*
Example 3	580.16(>500)*
Example 6	499.08(500)*
Example 28	170.76(240.52)*
Example 25	208.05(240.52)*
Example 29	255.45(240.52)*
Example 8	220.32(145.61)*
Example 26	114.64(145.61)*
Example 30	178.72(145.61)*
Example 27	112.37(145.61)*
Example 24	124.39(145.61)*
Example 1	499.08(500)*

Example 2	499.08(500)*
Example 12	449.38(342.06)*
Example 4	144.49(163.07)*
Example 16	444.23(500)*
Example 17	322.65(330.66)*
Example 15	188.95(330.66)*
Example 32	113.42(135.84)*
Example 31	119.97(135.84)*
Example 7	134.94(240.96)*

* The value in brackets in the second column indicates the value for Benzydamine (1-benzyl-3-[3-(dimethylamino)propyloxy]-1*H*-indazole) in the same assay.

Table 4

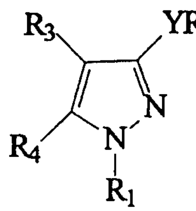
Compound of Example	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	Value for benzydamine in the same assay	IC_{50} for Inhibition of Platelet Aggregation (μM)
38	152.37	136.04	
39	182.16	136.04	35
40	147.30	136.04	100
43	149.75	136.04	
35	163.50	136.04	75
36	159.47	153.3	
44	167.41	152.19	1.5
33	180.72	103.86	
37	473.11	363.93	1
42	148.51	156.33	10
41	378.85	364.28	60
34	246.10	296.51	
46	190.88	192.81	2
47	176.98	194.5	
48	182.33	193.97	
49	204.33	194.6	
50	159.77	194.84	3
51	164.51	193.54	3
52	173.53	192.8	2

Compound of Example	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	Value for benzydamine in the same assay	IC_{50} for Inhibition of Platelet Aggregation (μM)
53	150.65	193.14	5
45	212.41	169.93	10+
54	122.40	170	5
55	130.72	169.77	10+
56	146.27		7
57	182.33	170.4	6.5
58	154.24	169.5	4
59	155.26	170.62	
60	208.08	170.56	10+
61	285.00	170.66	5
62	157.94	169.83	5
63	125.41	169.47	5
64	129.50	170.39	10+
65	204.78	276.73	10+
66	196.02	276.08	4
67	234.23	275.56	6
68	222.59	274.8	4
69	193.23	272.15	5
81	192.41	170.27	8
70	115.25		5.5
71	131.60		10+
82	245.24	326.99	6.5
83	288.05	327.3	2
84	336.33	329.74	10+
85	123.63	228.94	
86	340.37	327.28	5
87	377.32	328.1	8
88	320.66	327.2	2
89	388.99	329.65	2
100	182.21	227.76	6.5
72	197.44	227.00	10+
73	148.78	153.38	6
74	125.87	153.5	10+
75			5
90			3
91	282.55	227.86	1.75
92	173.6	228.42	10+
93	122.56	226.96	5

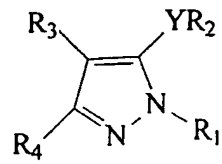
Compound of Example	1st Test cGMP Change with 1µM cpd (NO Donor Present), % of DEANO response	Value for benzydamine in the same assay	IC_{50} for Inhibition of Platelet Aggregation (µM)
94	121.09	228.47	7
95	169.4	228.92	6
96	122.5	227.85	10+
97	546.74	227.81	0.5
98	194.75	229.12	10+
101	99.44		10+
102	98.07	208.66	no activity
103	126.86	226.54	10+
104	156.08	229.53	10+
105	121.91	230.02	10+
106	128.8	230	7.5
107	127.94	228.46	10+
108	116.79	228.82	5.5
109	129.67	177.63	
110	126.54	178.22	
111	126.13	178.22	
112	134.67	177.2	
113	169.55	302.77	
114	235.87	109.71	10+
115	213.68	109.58	2
116	112.06	109.58	
99	144.77	176.55	
117			
118			

CLAIMS

1. Use of a compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the activation of soluble guanylate cyclase:



(Ia)



(Ib)

wherein:

Y is: -O-, $-CH_2-$ or -NH-;

R_1 is: hydrogen, aryl, heteroaryl, 3- to 6- membered heterocyclyl, $-(C_1-C_4$ alkyl)-R wherein R is aryl, heteroaryl or 3- to 6- membered heterocyclyl, C_1-C_4 alkyl, $-CONA'_2$, -COA" or $-SO_2A"$ wherein each A' is the same or different and is selected from H, C_1-C_4 alkyl and aryl and each A" is the same or different and is selected from C_1-C_4 alkyl and aryl;

R_2 is: (a) when Y is -O-: $-XNMe_2$ or -XNHMe wherein X is an alkylene group having from 3 to 5 carbon atoms or R_2 is 2-hydroxymethylfuran-5-yl-methyl or -WB wherein W is an alkylene group having from 1 to 5 carbon atoms and B is a N-containing heterocyclic group;

(b) when Y is $-CH_2-$: $-XNMe_2$ or -XNHMe wherein X is as defined above; and

(c) when Y is -NH-: $-XNMe_2$ or -XNHMe wherein X is propylene; and

R_3 and R_4, are either:

(a) the same or different and selected from $-CO_2A'$ wherein A' is as defined above, $-CF_3$, $-CCl_3$, halogen, C_1-C_4 alkoxy, $-(C_1-C_4$ alkyl)-aryl, $-(C_1-C_4$ alkyl)-heteroaryl, hydrogen, C_1-C_4 alkyl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl, $-SO_2NA'_2$ wherein A' is as defined above, and $-CONZ_1Z_2$ wherein Z_1 and Z_2, which are the

same or different, represent H, C_1-C_4 alkyl, aryl, heteroaryl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl or -(C_1-C_4 alkyl)-R wherein R is aryl, heteroaryl, 3- to 6- membered heterocyclyl or C_3-C_6 carbocyclyl, or Z_1 and Z_2, together with the nitrogen atom to which they are attached, denote a 5- or 6- membered N-containing heterocyclic group; or

(b) different, one of R_3 and R_4 being aryl or heteroaryl and the other being as defined above

or R_1 and R_2 are as defined above and R_3 and R_4 together form the divalent group, -$(CH)_4$-, which group is optionally substituted.

2. Use according to claim 1, wherein R_1 is hydrogen; aryl; heteroaryl, - (linear C_1-C_4 alkyl)-R in which the alkyl moiety is unsubstituted at the α position and R is aryl or heteroaryl; linear C_1-C_4 alkyl optionally substituted other than at the α position with hydroxy, halogen, -CF_3, -CCl_3, -NA'_2, -CO_2A' or -NH-CO-(C_1-C_4 alkyl), or R_1 is -$CONA'_2$; - COA" or -$SO_2A"$; wherein A' and A" are as defined in claim 1.

3. Use according to claim 2 wherein R_1 is hydrogen, -(CH_2)-aryl, -(CH_2)-heteroaryl, aryl, 3-hydroxy-n-propyl, 3-dimethylamino-n-propyl, 2-phenylethyl, 2-(CO_2Me)-ethyl, -$CONMe_2$, -COMe, -COPh or -SO_2Me.

4. Use according to any one of the preceding claims wherein R_2 is -$XNMe_2$ wherein X is an alkylene group having 3 or 4 carbon atoms or R_2 is -WB wherein W is an alkylene group having 1, 2, 3, 4 or 5 carbon atoms and B is (a) a pyridyl, piperidyl, pyrrolidinyl, piperazinyl or imidazolyl group optionally substituted where appropriate on the nitrogen atom with a methyl group or (b) a benzimidazolyl group optionally substituted on the benzene ring with halogen.

5. Use according to claim 4 wherein R_2 is -$(CH_2)_3NMe_2$ or -$(CH_2)_4NMe_2$.

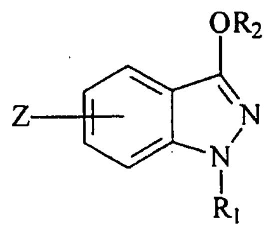
6. Use according to any one of the preceding claims wherein R_3 is hydrogen, C_1-C_4 alkyl, aryl or -(C_1-C_4 alkyl)-aryl.

7. Use according to any one of the preceding claims wherein R_4 is -CO_2A' wherein A' is as defined in claim 1, -$CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined in claim 1, C_1-C_4 alkyl, -CF_3, -CCl_3, halogen, C_1-C_4 alkoxy, aryl, heteroaryl, -(C_1-C_4 alkyl)-aryl or (C_1-C_4 alkyl)-heteroaryl.

8. Use according to any one of the preceding claims wherein R_4 is

$-CO_2H$, $-CO_2Me$, phenyl, oxadiazolyl, furanyl, pyridyl, C_1-C_4 alkyl, -(C_1-C_2 alkyl)-phenyl, or $-CONZ_1Z_2$ wherein Z_1 and Z_2 are as defined in claim 1.

9. Use according to any one of claims 1 to 5 wherein the compound of formula (Ia) is a compound of formula (Ic):



(Ic)

in which R_1 and R_2 are as defined in any one of claims 1 to 5 and Z denotes one or more selected from hydrogen, aryl, heteroaryl, -(C_1-C_4 alkyl)-R wherein R is aryl or heteroaryl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, nitro, cyano, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, $-NA'_2$, $-CO_2A'$ and -NH-CO-A' wherein A' is as defined in claim 1.

10. Use according to any one of the preceding claims wherein each A' is hydrogen, methyl or phenyl and each A" is methyl or phenyl.

11. Use according to claim 1 wherein the compound of formula (Ia) or (Ib) or said salt thereof is selected from:

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole-5-carboxylic acid;

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-methylaminocarbonyl-1*H*-pyrazole;

3-(3-Dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole;

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-phenyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-dipropylaminocarbonyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(N-morpholinocarbonyl)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-trifluoromethyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(dimethylaminocarbonyl)-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-(benzylaminocarbonyl)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-pyrazole

3-(2-(1-Methyl-2-pyrrolidinyl)ethyloxy)-5-phenyl-1*H*-pyrazole

3-(1-Methyl-3-piperidinyl)methyloxy-5-phenyl-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-4-phenyl-1*H*-pyrazole

1-Benzyl-3-(5-hydroxymethyl-2-furyl)methyloxy-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1-phenyl-1*H*-indazole

1-Benzyl-3-(4-dimethylaminobutyloxy)-1*H*-indazole

1-Acetyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1-(3-hydroxypropyl)-1*H*-indazole

1-Benzoyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1-(2-phenylethyl)-1*H*-indazole

(3-Dimethylaminopropyloxy)-1-methylsulfonyl-3-1*H*-indazole

1-(3-Dimethylaminopropyl)-3-(3-dimethylaminopropyloxy)-1*H*-indazole

3-(3-Dimethylaminopropyloxy)-1-(2-methoxycarbonylethyl)-1*H*-indazole

1-Benzyl-(3-dimethylaminopropyloxy)-4-methyl-1*H*-indazole

1-Benzyl-(3-dimethylaminopropyloxy)-6-methyl-1*H*-indazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-indazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole

1-Benzyl-5-(3-dimethylaminopropyloxy)-3-phenyl-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-1-methyl-1*H*-indazole

5-Phenyl-3-(4-pyridinylmethyloxy)-1*H*-pyrazole

3-(4-Dimethylaminobutyl)-5-phenyl-1*H*-pyrazole

3-(3-Dimethylaminopropylamino)-5-phenyl-1*H*-pyrazole

1-Benzyl-3-(5-dimethylaminopentyloxy)-1*H*-indazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-methyl-1,2,4-oxadiazol-5-yl]-1*H*-pyrazole

1-Benzyl-3-(3-dimethylaminopropyloxy)-5-[3-phenyl-1,2,4-oxadiazol-5-yl]-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-(3-furyl)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-(4-pyridyl)-1*H*-pyrazole

1,5-Diphenyl-3-(3-dimethylaminopropyloxy)-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-4-benzyl-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-benzyl-1*H*-pyrazole

3-(3-Dimethylaminopropyloxy)-5-ethoxycarbonylethyl-1*H*-pyrazole

3-(3′-Dimethylamino-1′-propoxy)-5-(3′,4′,5′-trimethoxyphenyl)-1*H*-pyrazole

5-Phenyl-3-(3-pyrrolidin-1-yl)-propyloxy)-1*H*-pyrazole

3-(3-Dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid methyl ester

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-5-hydroxymethyl-1*H*-pyrazole

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,4,5- trimethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-dimethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2-chloro-4-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-indol-5-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid thiazol-2-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-trifluoromethoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3,5-difluoro-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1*H*-benzoimidazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (1-phenyl-1*H*-pyrazol-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4,5,6,7-tetrahydro-benzothiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-[1,2,3]thiadiazol-4-yl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-oxazol-5-yl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-phenyl-thiazol-2-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-fluoro-5-trifluoromethyl-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid benzo [1,2,5]thiadiazol-4-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-2-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-4-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (2,2,4-trimethyl-2,3-dihydro-benzofuran-7-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (3-chloro-4-methoxy-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-bromo-phenyl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid quinolin-3-ylamide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid (4-methoxy-biphenyl-3-yl)-amide

1-Benzyl-3-(3-dimethylamino-propoxy)-1*H*-pyrazole-5-carboxylic acid isoquinolin-1-ylamide

1,5-Dibenzyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(3′,4′-Dichlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Trifluoromethyl-4′-fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-(Trifluoromethoxy)benzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(3′-Bromobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(2′-Fluorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(2′-Chlorobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Nitrobenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(4′-Phenylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-Piperonyl-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-([1-(4′-Chlorobenzyl)-1*H*-imidazol-2-yl]methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(Thiophen-2′-methyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

2-(2′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-2*H*-pyrazole

1-(2′-Methoxybenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

1-(3′-Methylbenzyl)-3-(3′-dimethylamino-1′-propoxy)-5-benzyl-1*H*-pyrazole

and pharmaceutically acceptable salts thereof.

12. Use according to claim 1, wherein R_1 is hydrogen, aryl, -(C_1-C_4 alkyl)-aryl, C_1-C_4 alkyl, -CONA$'_2$, -COA$''$ or -SO_2A$''$ wherein each A$'$ is the same or different and is selected from H, C_1-C_4 alkyl and aryl and each A$''$ is the same or different and is selected from C_1-C_4 alkyl and aryl and R_3 and R_4 are either:

(a) the same or different and selected from -CO_2H, -CO_2-aryl, -CF_3, CCl_3, halogen, C_1-C_4 alkoxy, -(C_1-C_4 alkyl)-aryl, hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3- to 6- membered heterocyclyl, -SO_2NA$'_2$ wherein A$'$ is as defined above, or -CONZ_1Z_2 wherein Z_1 and Z_2, which are the same or different, represent H, C_1-C_4 alkyl, aryl or -(C_1-C_4 alkyl)-aryl or Z_1 and Z_2, together with the nitrogen atom to which they are attached, denote a 5- or 6- membered N-containing heterocyclic group; or

(b) different, one of R_3 and R_4 being aryl or heteroaryl and the other being as defined above,

or R_3 and R_4 together form the divalent group -$(CH)_4$-, which group is optionally substituted.

13. Use according to any one of the preceding claims, wherein the medicament is for use as a vasodilator or to inhibit platelet aggregation.

14. Use according to any one of claims 1 to 13 wherein the medicament is for use in the treatment or prevention of a peripheral vascular disease, glaucoma, preeclampsia, Raynaud's Syndrome, stroke or erectile dysfunction.

15. A compound of the formula (Ia) or (Ib), as defined in any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, except for:

(a) compounds of formula (Ia), in which Y is -O-, R_3 and R_4 together form a benzene ring optionally substituted with a chlorine atom, an amino group, a methoxy group or a nitro group, R_2 is $-XNMe_2$ wherein X is ethylene or propylene and R_1 is C_1-C_4 alkyl, phenyl, benzyl or 2-phenylethyl;

(b) compounds of formula (Ia) in which Y is -O-, R_1 and R_3 are each a phenyl group optionally substituted with an alkyl group, an alkoxy group or a halogen atom, R_4 is hydrogen, and R_2 is $-XNMe_2$ or -XNHMe wherein X is ethylene or propylene or R_2 is -WB wherein W is ethylene or propylene and B is a 5- or 6- membered N-containing heterocycle, linked to the group W via the N atom; and

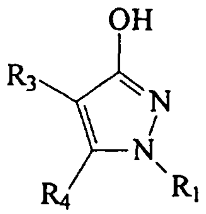
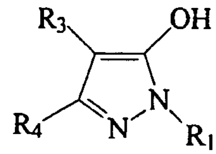
(c) compounds of formula (Ia) in which Y is -O-, R_3 and R_4 together form a benzene ring, R_2 is $-(CH_2)_3NMe_2$ and R_1 is hydrogen or $-(CH_2)_3NMe_2$.

16. A compound of formula (I) as defined in claim 15, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body by therapy.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a compound of formula (I) as defined in claim 15 or a pharmaceutically acceptable salt thereof.

18. A process for the preparation of a compound of formula (Ia) or (Ib), as defined in claim 15, in which Y is -O-, or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (IIa) or (IIb)

 (IIa)  (IIb)

in which R_1, R_3 and R_4 are as defined in claim 14, with a compound of formula (III):

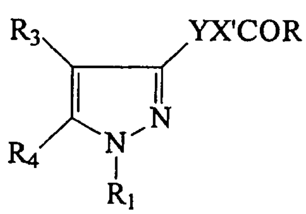
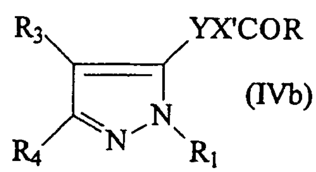
$X\text{-}R_2$ (III)

in which X is OH or a leaving group and R_2 is as defined in claim 14; and

(b) optionally salifying the thus obtained compound of formula (Ia) or (Ib).

19. A process for the preparation of a compound of formula (Ia) or (Ib), as defined in claim 15, in which Y is $-CH_2-$ or -NH-, which process comprises:

(a) reducing a compound of formula (IVa) or (IVb)

 (IVa)  (IVb)

wherein R^1, R^3 and R^4 are as defined in claim 14; and

(b) optionally salifying the thus obtained compound of formula (Ia) or (Ib).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03663

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 A61K31/416 A61K31/4155 A61K31/5377 A61K31/454
A61K31/4439 A61K31/4709 A61K31/428 A61K31/427 A61K31/4275
A61K31/4184 A61K31/422 A61K31/433 A61K31/4178 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 197412 Derwent Publications Ltd., London, GB; AN 1974-21885v XP002133681 & JP 49 007279 A (NIKKEN CHEM. CO. LTD), 22 January 1974 (1974-01-22) See Derwent abstract in light of formulas of Japanese patent application — -/--	15-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2000	31/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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INTERNATIONAL SEARCH REPORT

Int. ...onal Application No
PCT/GB 99/03663

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P9/10 A61P9/08 A61P27/06 C07D231/56 C07D231/20 C07D231/22 C07D413/04 C07D401/12 C07D401/04 C07D405/12 C07D405/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZONI ET AL.: "Proprieta' farmacologiche di alchil-derivati dell'1-(m-trifluorometilfenil)-3-idrossi-1 H-indazolo" FARMACO, vol. 25, no. 5, 1970, pages 386-405, XP000876729 see page 387 Table I compounds IFT998 and IFT910	15-17
X	DATABASE WPI Week 198630 Derwent Publications Ltd., London, GB; AN 1986-194723 XP002133682 & JP 61 129124 A (KUREHA CHEM. IND. CO LTD), 17 June 1986 (1986-06-17) abstract	15-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ES 330 731 A (J. A. BOFILL AUGE) 22 August 1968 (1968-08-22) the whole document	15,18
X	SOGA ET AL.: "Synthesis of 1-substitutd 3-(dialkylaminoalkoxy)-4,5,6,7-tetrahydro-1H-indazoles" BULL. CHEM. SOC. JPN, vol. 53, 1980, pages 825-826, XP000876596 cited in the application see page 825 compound 4b	15
A		15
X	ZONI ET AL.: "Sintesi di alchil-derivati dell'1-(m-trifluorometilfenil)-3-idrossi-1 H-indazolo" BOLL. CHIM. FARM., vol. 107, no. 10, 1968, pages 598-605, XP000879272 see page 599 compounds X,XI and XII	15
X	NAGASAKI ET AL.: "Metabolism of Benzydamine hydrochloride" CHEM. PHARM. BULL., vol. 19, no. 7, 1971, pages 1511-1513, XP000879139 see page 1512 compound "HO-benzyl-BZY"	15
X	CORSI : "Preparazione di possbili metaboliti della benzidamina" BOLL. CHIM. FARM.-, vol. 111, no. 9, 1972, pages 566-572, XP000879068 see page 566 compounds I and II	15
X	BARBAZ ET AL.: "1-substituted 3-aminoalkoxy-4,5-cycloalkylparazoles with central nervous system depressant activity" J. MED. CHEM., vol. 15, no. 10, 1972, pages 1027-1029, XP000876634 see page 1028 Table II compound 13	15
A	FR 2 301 250 A (LABORATOIRES ROGER BELLON) 17 September 1976 (1976-09-17) cited in the application the whole document & FR 7 505 524 A	15-18

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JANSEN ET AL.: "Antithrombotische Wirkung von Benzydamin" ARZNEI. FORSCHUNG, vol. 37, no. 5a, 1987, pages 626-628, XP000876724 the whole document ---	1-5,13
A	WEGENER ET AL.: "Activation of soluble guanylyl cyclase by YC-1 in aortic smooth muscle but not in ventricular myocardium from the rat" BR. J. PHARMACOL., vol. 122, no. 7, December 1997 (1997-12), pages 1523-1529, XP000878915 the whole document ---	1-3,9, 12-14
A	KO ET AL.: "YC-1, anovel activator of platelet guanylate cyclase" BLOOD, vol. 84, no. 12, 15 December 1994 (1994-12-15), pages 4226-4233, XP000878904 the whole document ---	1-3,9, 12-14
A	TENG ET AL.: "YC-1, a nitric oxide-independent activator of soluble guanylate cyclase, inhibits platelet-rich thrombosis in mice" EUR. J. PHARMACOL., vol. 320, no. 2-3, 12 February 1997 (1997-02-12), pages 161-166, XP000878912 the whole document ---	1-3,9, 13,14
A	SCHMIDT ET AL.: "Potentiation of NO and Endothelium-independent relaxation through a long-lasting soluble guanylyl cyclase stimulation by YC-1 (3-(5-hydroxymethyl-2'-furyl)-1-benzyl-indazol)" BR. J. PHARMACOL., vol. 123, no. proc. suppl., March 1998 (1998-03), page 299p XP000878914 abstract ---	1-3,9, 13,14
A,P	WO 98 58633 A (QUEEN'S UNIVERSITY AT KINGSTON) 30 December 1998 (1998-12-30) abstract page 3, line 25 page 16 page 17, line 5 ---	1,13,14

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 500 230 A (J.A. NATHANSON) 19 March 1996 (1996-03-19) abstract column 3 -column 4	1,13,14
A	WO 98 16507 A (BAYER AG) 23 April 1998 (1998-04-23) page 2 page 40 -page 44	1,13,14
A	SUGRUE: "New approaches to antiglaucoma therapy" J. MED. CHEM., vol. 40, no. 18, 1997, pages 2793-2809, XP000878913 page 2800, right-hand column, paragraphs 3,4 page 2802	1,13,14
A	CATANESE ET AL.: "Effects of benzydamine and other non-steroidal antiinflammatory drugs on platelet aggregation induceds by; arachidonic acid, ADP and collagen" BOLL. CHIM. FARM., vol. 125, no. 7, 1986, pages 228-233, XP000879042 page 232	13
A	DE 196 49 460 A (BAYER AG) 28 May 1998 (1998-05-28) the whole document	1,13,14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03663

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
SEE FURTHER INFORMATION PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10,12-19 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely on the compounds of claim 11 and of the examples (p. 30-65).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03663

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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